IgG4-Related Sclerosing Cholangitis

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Editors

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Preface

IgG4-related disease (IgG4-RD) is a fibro-inflammatory and immune-mediated condition with a tendency toward the tumefaction that mimics malignant or inflammatory disorders. IgG4-RD was first proposed as a systemic disease in 2003 following the recognition that a high percentage of patients with autoimmune pancreatitis (AIP) had extrapancreatic lesions that shared similar histopathological findings consisting of abundant infiltration of IgG4-positive plasma cells and lymphocytes and fibrosis. IgG4-RD can affect almost any organ; only a single organ is clinically involved in some cases, whereas others show effects on two or more organs simultaneously or metachronously. IgG4-RD is also characterized by elevation of serum IgG4 levels and steroid responsiveness.

IgG4-related sclerosing cholangitis (IgG4-SC) is the biliary manifestation of IgG4-RD. Although about 60% of patients with IgG4-RD have biliary lesions in the proximal and/or distal bile ducts, the inclusion of a distal biliary stricture isolated to the intrapancreatic portion associated with AIP in the definition of IgG4-SC remains under debate.

When stenosis develops in the hilar or intrahepatic bile duct, the cholangiographic appearance is similar to that of primary sclerosing cholangitis (PSC), a progressive disease for which liver transplantation is the only effective curative treatment. Another important disease that should be differentiated from IgG4-SC is cholangiocarcinoma. The radiological findings of IgG4-SC involving the hilar bile duct are quite similar to those of hilar cholangiocarcinoma. Since IgG4-SC responds well to steroid therapy, it is necessary to differentiate between the two diseases in order to provide the most appropriate treatment regimen. Although clinical diagnostic criteria of IgG4-SC were proposed in 2012, its diagnosis is still a clinical challenge and requires a multidisciplinary approach, in which serology, imaging, and histology play crucial roles.

Currently, systemic glucocorticoid is the first-line agent for IgG4-SC; however, frequent relapse of the disease remains a problem. Recently, rituximab has been successfully used to treat patients with IgG4-SC who showed resistance to or side effects from steroid treatment.

The goal of this book is to raise awareness of IgG4-SC and provide practicing physicians the principles for its diagnosis and management by clarifying its current concept and covering all aspects of its clinical, serological, histopathological, imaging, therapeutic, and prognostic features in the world. We are deeply grateful to all the authors for their painstaking writing and

contributions in preparing this concise and informative book. The publisher has also made a significant contribution to this book and has turned out an impressive volume with illustrations of the highest quality.

Tokyo, Japan — Terumi Kamisawa
Seoul, South Korea — Myung-Hwan Kim

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Overview

1

Takahiro Nakazawa, Shuya Simizu, Tadashi Toyohara, Hiromichi Araki, and Katumi Hayashi

Introduction

Recently, IgG4-related sclerosing cholangitis (IgG4-SC) has attracted much attention with the emergence of clinical characteristics that distinguish it as a new clinical entity. IgG4-SC has a cholangiographic appearance similar to that of primary sclerosing cholangitis (PSC) and cholangiocarcinoma [1]. IgG4-SC respond well to steroid therapy (Fig. 1.1). In contrast, PSC is progressive and resistant to therapy, eventually involving both the intra- and extrahepatic bile ducts and resulting in biliary cirrhosis [2]. The value of steroid therapy has been questioned, and liver transplantation is the only effective measure for cure. Establishment of the concept of autoimmune pancreatitis (AIP) has meant that unnecessary surgery in the event of misdiagnosis of pancreatic

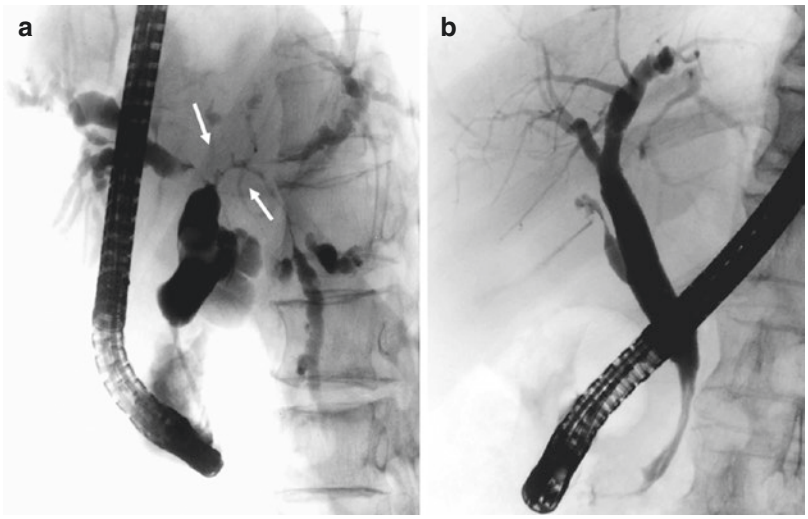

Fig. 1.1 Steroid therapy for type 2 IgG4-SC. (**a**) ERC showed diffuse stenosis in intrahepatic bile duct. (**b**) The diffuse stenosis dramatically improved by steroid therapy

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carcinoma can be avoided. Similarly, once a diagnosis of IgG4-SC can be established, then both liver transplantation under a diagnosis of PSC and hepatectomy under a diagnosis of cholangiocarcinoma can be avoided. Therefore, it is necessary to discriminate these diseases before choosing the most appropriate therapy.

Characteristic Features of IgG4-Related Sclerosing Cholangitis

Elevated serum IgG4 level is a characteristic feature of IgG4-SC [3]. In patients with IgG4-SC, the pancreas was the most common organ involved other than the bile duct. Patients with IgG4-SC show multiorgan involvement, including sclerosing sialadenitis, retroperitoneal fibrosis, and mediastinal lymphadenopathy. Based on histological and immunohistochemical examination of various organs, clinicopathological entity called "IgG4-related systemic disease" was proposed [4]. IgG4-SC is considered to be a biliary manifestation of IgG4-related disease. IgG4-RD including IgG4-SC was originally suspected to be an autoimmune disorder based on its frequent association with ANA positivity and steroid responsiveness. However, this possibility has been questioned. Unlike classic autoimmune disorders, patients with IgG4-RD are older (median age, 67 years) and 80% are male.

Two diagnostic criteria have been used in the diagnosis of IgG4-SC [5, 6]. Both criteria consist of imaging, serology, histology, other organ involvement, and responses to steroid therapy. If IgG4-SC is associated with AIP or other IgG4-related diseases, diagnosis is not so difficult. Otherwise, isolated IgG4-SC is difficult to diagnose. We should keep in mind several points for precise diagnosis. First, 10% of IgG4-SC cases show lower serum IgG4 level than cutoff value. Second, IgG4-SC show characteristic pathological findings but acquiring enough pathological sample for evaluation by bile duct biopsy is difficult because of superficial nature. Third, if the diagnosis remains nonconclusive, steroid trials may be considered; however, the possibility of malignancy should be carefully excluded before commencing immunosuppression.

Imaging suggestive for IgG4-SC are summarized in Fig. 1.2. We should evaluate imaging of IgG4-SC from two aspects, character of stenosis

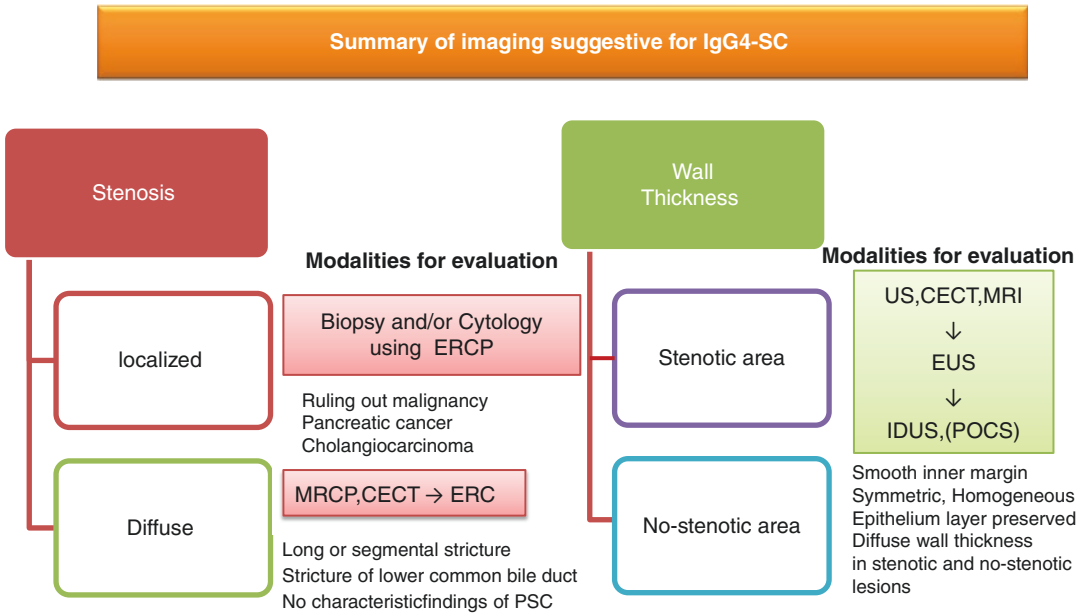


Fig. 1.2 Images suggestive for IgG4-SC. If stenosis is localized, bile duct biopsy is necessary in order to rule out cholangiocarcinoma. If stenosis is diffusely distributed, cholangiography can discriminate IgG4-SC from PSC. Diffuse bile duct wall thickness without injury of epithelium is characteristic for IgG4-SC

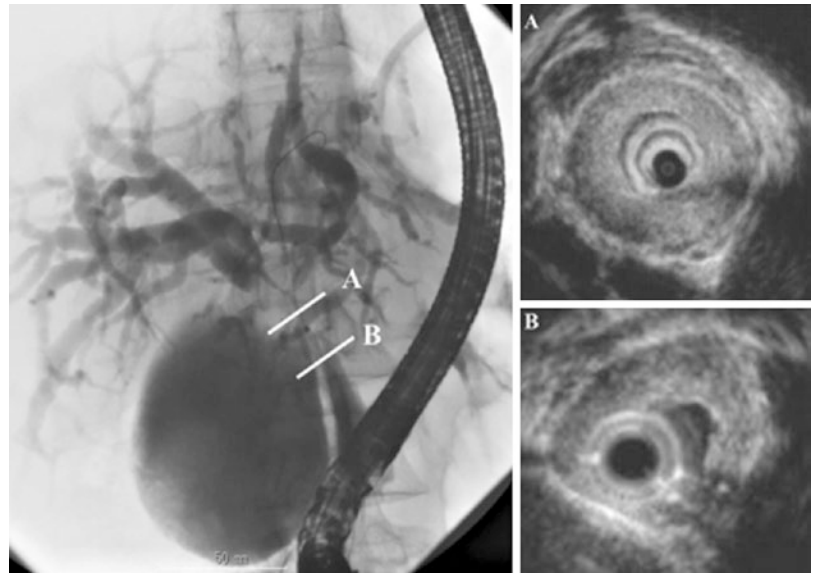


Fig. 1.3 Type 3 IgG4-SC and IDUS findings. ERC showed stenosis at the hilar hepatic lesion. IDUS showed symmetric and homogeneous wall thickness without epithelial injury both in the stenotic and non-stenotic lesions

and wall thickness. Imaging clearly reflects pathological characters that inflammation occurs mainly in stroma with normal mucosa surface. Severe infiltrating inflammatory cells induce long stricture in cholangiography on the contrary to short stricture due to fibrosis in PSC. If stenosis is localized, bile duct biopsy is necessary in order to rule out cholangiocarcinoma. If stenosis is diffusely distributed, cholangiography can discriminate IgG4-SC from PSC. If stenosis is localized, ruling out cholangiocarcinoma by bile duct biopsy is necessary. Bile duct wall thickness without injury of epithelium can be detected by intraductal ultrasonography (IDUS) (Fig. 1.3) or endoscopic ultrasonography (EUS).

The treatment strategy is basically similar to that for type 1 AIP. Steroid (prednisone at a dose of 0.6 mg/Kg/day) is the treatment of choice and generally leads to the rapid and consistent induction of disease remission. Although disease relapse is relatively common, IgG4-SC is considered a "benign" disease with a low risk of liver failure and biliary malignancy [7].

History and Nomenclature

Before the concept of AIP was established, the terms primary sclerosing cholangitis and sclerosing cholangitis associated with chronic pancreatitis/pancreatic pseudotumor were used. These disease entities were referred to as atypical primary sclerosing cholangitis to discriminate them from classic PSC [8]. The terms sclerosing cholangitis associated with AIP and autoimmune pancreatocholangitis have been applied in the context of AIP, and the terms lymphoplasmacytic sclerosing cholangitis, IgG4-related sclerosing cholangitis [9], and IgG4-associated cholangitis [6] have been employed in the context of IgG4-related autoimmune diseases based of their characteristic pathological changes.

Concept of Sclerosing Cholangitis

Classification of Sclerosing Cholangitis

Sclerosing cholangitis has been classified into two categories: PSC and secondary sclerosing cholangitis (SSC). IgG4-SC has sometimes been described as an isolated biliary tract lesion, even in the absence of pancreatic involvement, and has thus been established as a distinct clinical entity. Therefore, sclerosing cholangitis is now classified into three categories: PSC, IgG4-SC, and SSC [10, 11]. We have identified three reasons why IgG4-SC should be considered independently from other forms of SSC. First, steroid therapy is highly effective for IgG4-SC, in contrast to the other types of sclerosing cholangitis. Second, in comparison with the other forms,

IgG4-SC is frequently encountered in daily clinical practice. Third, the characteristics of IgG4-SC need to be fully discriminated from those of the other three intractable diseases, that is, pancreatic cancer PSC, and cholangiocarcinoma.

With regard to the diagnosis of sclerosing cholangitis, SSC should be ruled out first. Thereafter, IgG4-SC should be suspected; the serum IgG4 level, measured; and further exploration for pancreatic involvement or other IgG4-related systemic disease, conducted. Finally, compatibility with the criteria for PSC should be ascertained.

Primary Sclerosing Cholangitis

We have previously reported the differences between IgG4-SC and PSC [2]. Age at clinical onset was significantly older for patients with IgG4-SC. Among the chief complaints in IgG4-SC, obstructive jaundice, reflecting marked concentric stenosis of the large bile duct, was most frequently observed. However, approximately half of PSC patients in Japan are nonsymptomatic at diagnosis.

Secondary Sclerosing Cholangitis

SSC is a chronic cholestatic biliary disease that can develop after a diverse range of insults to the biliary tree. SSC is considered to develop as a consequence of known injuries or secondary to pathological processes of the biliary tree. The etiology of SSC can usually be identified, although the exact pathogenesis often remains speculative. The most frequently described causes of SSC are long-standing biliary obstruction, surgical trauma to the bile duct, and ischemic injury to the biliary tree in liver allografts.

Classification of IgG4-SC

Cholangiographic Classification

IgG4-SC displays various cholangiographic features similar to those of pancreatic cancer, PSC, and cholangiocarcinoma. The characteristic features of IgG4-SC can be classified into four types based on the stricture regions revealed by cholangiography and differential diagnosis (Fig. 1.4) [1]. Type 1 IgG4-SC displays stenosis only in the lower part of the common bile duct and thus should be differentiated from chronic pancreatitis, pancreatic cancer, and cholangiocarcinoma. Type 2 IgG4-SC, in which stenosis is diffusely distributed throughout the intrahepatic and extrahepatic bile ducts, should be differentiated from PSC and is further subdivided into two subtypes: type 2a, characterized with narrowing of the intrahepatic bile ducts with prestenotic dilation, and type 2b, characterized by the narrowing of the intrahepatic bile ducts without prestenotic dilation and reduced bile duct branches, which is caused by marked lymphocytic and plasmacytic infiltrations into the peripheral bile ducts. Differential diagnosis between type 2a IgG4-SC and PSC is possible by endoscopic retrograde cholangiography (ERC) [12]. However, differential diagnosis between type 2b IgG4-SC and PSC with pruned tree appearance is difficult by ERC. Type 3 IgG4-SC is characterized by stenosis in the hilar hepatic lesions and the lower part of the common bile duct. Type 4 IgG4-SC presents with strictures of the bile duct only in the hilar hepatic lesions. The cholangiographic findings of types 3 and 4 IgG4-SC should be discriminated from those of cholangiocarcinoma. Bile duct biopsy is necessary for differential diagnosis between type 3 and 4 IgG4-SC and cholangiocarcinoma [13].

Inclusion of type 1 IgG4-SC into the IgG4-SC category has been disputed. Some researchers claim that the stricture of the lower common bile duct, which is observed in type 1 IgG4-SC, is caused by compression due to AIP [14]. This claim is based on the fact that type 1 IgG4-SC was not found in some cases of focal-type AIP with only body and tail involvement. On the contrary, others claim that type 1 IgG4-SC should be classified as one of the IgG4-SC types because of the following reasons. First, pathological examination of the bile duct wall obtained from surgically resected samples showed abundant IgG4-positive plasma cell infiltration, storiform

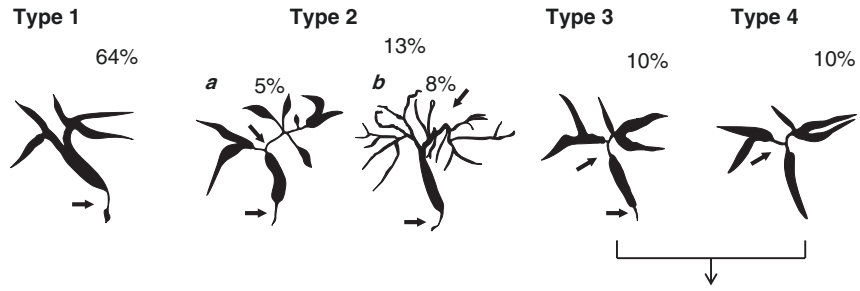
fibrosis, and obstructive phlebitis, which are characteristics of IgG4-SC-associated inflammation [9]. Second, the results of an IDUS study showed continuous thickening of the bile duct wall from the intrapancreatic to the extrapancreatic bile duct [13]. Third, isolated type 1 IgG4-SC has been reported [15]. In fact, it is difficult to identify which is the major factor contributing to the thickening of the bile duct wall—inflammation of the bile duct or compression due to AIP.

IgG4-SC With/Without AIP

IgG4-SC is frequently associated with AIP. A Japanese multicenter study revealed that 458 (87%) of 527 patients with IgG4-SC had AIP [7]. This association with AIP is useful when diagnosing IgG4-SC. However, some IgG4-SC cases are isolated from AIP and are difficult to diagnose [16].

Most reported cases of isolated IgG4-SC have hilar biliary strictures. We evaluated 344 patients with IgG4-SC according to our cholangiographic classification [17]. A total of 329 (95.6%) of the 344 IgG4-SC cases were associated with AIP (244 of 246 type 1 IgG4-SC cases [99.2%]; 51 of 56 type 2 IgG4-SC cases [91.1%]; 34 of 42 type 3 and 4 IgG4-SC cases [81.0%]). Type 3 and 4 IgG4-SC cases showed lower frequencies of association with AIP.

Isolated IgG4-SC with an intrapancreatic biliary stricture (type 1 IgG4-SC) is very rare. We encountered five cases of type 1 IgG4-SC that were not associated with AIP [17]. None of our cases had an enlarged pancreas, and only one showed an atrophied pancreas. None of the cases had an irregular narrowing of the main pancreatic duct. Four cases had a normal main pancreatic duct, and one showed slight dilation of the main pancreatic duct. Thickening of the bile duct wall in lesions without a luminal stenosis, which is a characteristic finding of IgG4-SC, was detected by abdominal computed tomography (CT) in all five cases and by IDUS in three cases. The IgG4



	Type 1	Type 2	Type 3	Type 4
Differential diagnosis	Pancreatic cancer Bile duct cancer Chronic pancreatitis	Primary sclerosing cholangitis	Bile duct cancer Gallbladder cancer	
Useful modalities	IDUS* (bile duct) EUS-FNA** (pancreas) Biopsy (bile duct)	Liver biopsy Colonoscopy (R/O coexistence of IBD ***)	EUS (bile duct, pancreas) IDUS (bile duct) Biopsy (bile duct)	

* IDUS：Intraductal ultrasonography
** EUS-FNA：Endoscopic ultrasound-guided fine needle aspiration
*** IBD: Inflammatory bowel disease

Fig. 1.4 The cholangiographic classification, frequency of IgG4-SC and differential diagnosis. Stenosis is located only in the lower part of the common bile duct in type 1; stenosis is diffusely distributed in the intra- and extrahepatic bile ducts in type 2. Type 2 is further subdivided into two types. Extended narrowing of the intrahepatic bile ducts with prestenotic dilation is widely distributed in type 2a. Narrowing of the intrahepatic bile ducts without prestenotic dilation and reduced bile duct branches are widely distributed in type 2b; stenosis is detected in both the hilar hepatic lesions and the lower part of the common bile ducts in type 3; strictures of the bile duct are detected only in the hilar hepatic lesions in type 4. *IDUS* intraductal ultrasonography, *EUS-FNA* endoscopic ultrasound-guided fine needle aspiration, *IBD* inflammatory bowel disease

values of all three cases were within normal limits (<135 mg/dL). All three cases underwent surgery under suspicion of cholangiocarcinoma. The other two cases had high IgG4 values, and one case received steroid therapy. The other case was treated only with endoscopic biliary drainage. The pathological findings of the bile duct from surgical specimens of the three cases showed severe infiltration of lymphocytes, IgG4-positive plasmacytes, and prominent fibrosis, compatible with the findings of IgG4-SC, but no inflammatory changes compatible with AIP in adjacent pancreatic tissues. We concluded that isolated type 1 IgG4-SC cases are difficult to diagnose, particularly those with normal IgG4 values. We should be aware that isolated type 1 IgG4-SC are also one of the candidates in addition to a cholangiocarcinoma and pancreatic cancer when we diagnose a stenosis of intrapancreatic bile duct.

Early Stage/Advanced Stage

Advanced-stage IgG4-SC may sometimes be unresponsive to steroid therapy because cases of IgG4-SC show predominantly inflammatory nature at the early stage, followed by relatively less inflammation but marked fibrous scarring later in the course of the disease [18]. Similarly, AIP in advanced stage show sometimes calcification mimicking chronic pancreatitis, and stenosis of main pancreatic duct does not respond well to steroid therapy. This should be kept in mind when evaluating effectiveness of steroid therapy, especially in a steroid trial for IgG4-SC diagnosis.

Conclusion

Although disease relapse is relatively common, IgG4-SC is considered a "benign" disease with a low risk of liver failure and biliary malignancy. Therefore, differential diagnosis is important before starting treatment. As the concept of IgG4-SC prevails, our diagnostic ability has improved. Diagnosis of isolated IgG4-SC is still difficult. Bile duct biopsy and IDUS through ERCP are performed for ruling out cholangiocarcinoma and evaluating wall thickness. Further investigation for less invasive modality or more definite serological markers is necessary. New therapeutic strategies are also necessary because long-term steroid therapy induces several adverse events for aged people.

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2 Epidemiology

Atsushi Tanaka

Introduction

Immunoglobulin G4-related sclerosing cholangitis (IgG4-SC) is a relatively new disease entity, thus very limited data are currently available regarding its epidemiology. To date, several case series regarding clinical profiles of IgG4-SC have been published, including our study [1–3]; however, no epidemiological studies illustrating the incidence and prevalence of IgG4-SC have been conducted. In this review, epidemiological and clinical features of IgG4-SC are discussed in general and are based mainly on data in the Japanese population.

Prevalence and Incidence

Epidemiological data on IgG4-SC is currently not available. However, it can be extrapolated from that of autoimmune pancreatitis (AIP), which is another IgG4-related disease (IgG4-RD) of the gastrointestinal system and is frequently found as a comorbid disorder in patients with IgG4-SC. In 2011, Kanno et al. carried out a clinico-epidemiological survey of AIP in Japan, yielding an overall prevalence of 4.6 per 100,000 population and an annual incidence of 1.4 per 100,000 population [4]. In that study, a prevalence of IgG4-SC in patients with AIP was reported as 39%, and thus an overall prevalence and an annual incidence of patients who have both AIP and IgG4-SC is estimated as 1.8 and 0.5 per 100,000 population, respectively. Furthermore, our nationwide survey of IgG4-SC in 2015 demonstrated that the proportion of patients diagnosed as having both IgG4-SC and AIP was 87% of all IgG4-SC cases [3]. Thus, taking both studies together, an overall incidence and an annual prevalence is calculated to be 2.1 and 0.63 per 100,000 population, respectively. These estimated incidence and prevalence in Japan are less than half of those of AIP, and the overall number of patients with IgG4-SC in Japan is estimated at 2500. The prevalence and incidence in Western countries may be different to that in Japan, thus epidemiological studies in the Japanese population are warranted.

Case Series of IgG4-SC

Biliary involvement of AIP or IgG4-RD has been already reported in 2007 [5] and is regarded as a different clinical entity from primary sclerosing cholangitis (PSC) in terms of responses to corticosteroids [6]. However, the clinical, biochemical, and radiographic features of IgG4-SC have not been well characterized, probably because of the rarity of the disease and lack of globally accepted

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diagnostic criteria. In 2008, Ghazale et al. analyzed the large database of AIP patients at Mayo Clinic, Minnesota, USA, and described the clinical profiles and response to therapy in 53 patients with IgG4-associated cholangitis [1]. Huggett et al. conducted the largest case series of IgG4-SC in 2014 and reported that AIP and/or IgG4-SC was associated with significant morbidity and mortality in the cohort of 115 patients, which included 68 patients with IgG4-SC [2]. In 2012, we performed a nationwide survey of PSC and IgG4-SC in Japan and described the clinical characteristics of 43 patients with IgG4-SC without AIP or "solitary IgG4-SC" [7]. In 2015, we performed another nationwide survey on PSC and IgG4-SC in Japan, which enrolled all patients with IgG4-SC, irrespective of the presence or absence of AIP [3].

It is of note that the diagnostic criteria differed among these studies. In the case series from Mayo Clinic [1], IgG4-SC was diagnosed using a combination of biliary imaging and presence of AIP. The HISORt criteria (histology, pancreatic imaging, serology, other organ involvement and response to steroid therapy) were used for confirmation of the presence of AIP. Using these criteria, four patients did not show evidence of AIP ("solitary IgG4-SC") and were histologically diagnosed as having IgG4-SC. In the case series from the UK [2], IgG4-SC was diagnosed in a similar manner, using a combination of biliary imaging and confirmation of the absence of AIP as a comorbidity. In Japan, diagnosis of AIP was made using the Japan Pancreas Society criteria initially [8] and the HISORt criteria thereafter. In our case series in Japan, the clinical diagnostic criteria established by the Japanese Biliary Association in 2012 [9] was used. While definite, probable, or possible diagnosis was established using the criteria, only patients with a definite or probable diagnosis were included.

Demographics

The demographics of patients with IgG4-SC are summarized in Table 2.1. IgG4-RD is generally a male-dominant disease, and indeed male patients are dominant in all three reports. The proportion of male patients was 85%, 74%, and 83% in the USA [1], the UK [2], and Japan [3], respectively. The age at presentation was also similar among these three reports, indicating that those in their 60s are at the highest risk for developing IgG4-SC. In Fig. 2.1, distributions of age and sex at presentation are shown in 527 cases with IgG4-SC in Japan. The age ranged from 23.0–88.5 years, and unlike PSC, which can be difficult to differentiate from IgG4-SC in terms of biliary imaging, no patient developed IgG4-SC in childhood or adolescence. The age distribution was quite similar in both male and female patients, and the median age at diagnosis was 66.2 years. Therefore, although the diagnostic criteria might differ among the three-case series, the demographics of IgG4-SC are quite comparable.

Seeking Etiological Factors

Although case-control studies for clarifying the etiology of this enigmatic disease have not been carried out, preliminary data suggested a role of environmental triggers for developing IgG4-SC and AIP [10]. A questionnaire-based study revealed that a history of blue-color work was noted in 88% of patients with IgG4-SC and/or AIP in the Amsterdam cohort and in 61% of patients with IgG4-SC and/or AIP in the Oxford cohort, both of which were much higher than that in patients with PSC. Occupational antigens such as solvents, industrial and metal dusts, and pigments

Table 2.1 Epidemiological features of IgG4-SC

Region	Year	N	Male (%)	Age at presentation (years)
USA [1]	2008	53	85	62[a]
UK [2]	2014	68	74	61[b]
Japan [3]	2017	527	83	66[b]

[a]Average
[b]Median

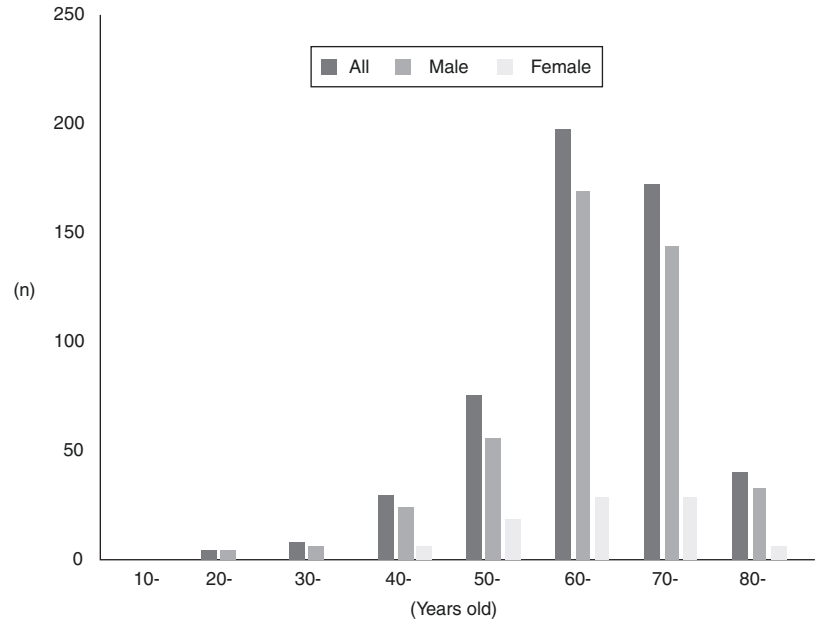

Fig. 2.1 Distribution of age at presentation, for patients with IgG4-related sclerosing cholangitis in Japan [3]

and oils, to which these patients could have been exposed, could be the triggers for developing IgG4-SC. Further investigations are warranted in other cohorts.

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Pathophysiology

3

Yoh Zen

Abbreviations

IgG4-AIP	IgG4-related autoimmune pancreatitis
IgG4-RD	IgG4-related disease
IgG4-SC	IgG4-related sclerosing cholangitis
PSC	Primary sclerosing cholangitis

Introduction

During the discovery process of IgG4-related disease (IgG4-RD), the bile duct appeared to be one of the target organs commonly affected by this condition [1–3]. Sclerosing cholangitis is a central biliary manifestation of IgG4-RD [1–3]. Although clinical manifestations of IgG4-RD vary widely among patients, underlying immune reactions and pathophysiology are supposed to be similar in any organs given the almost identical histopathological changes. Similar to other immune-mediated conditions, a likely pathogenetic mechanism is that the disease develops in genetically susceptible individuals exposed to external or endogenous antigens [4]. In this review, our current understanding of the molecular features of this emerging biliary disease is summarized. Data obtained from not only IgG4-related sclerosing cholangitis (IgG4-SC) but also IgG4-RD at other anatomical sites are discussed [4, 5].

Genetic Susceptibility

Genetic risks of IgG4-RD have been investigated most extensively in patients with IgG4-related autoimmune pancreatitis (IgG4-AIP). Although the HLA serotypes DRB1*0405 and DQB1*0401 are known to increase susceptibility of IgG4-AIP in Japanese populations [6], this association has not been proven in other ethnicities [7]. Five non-HLA genes, single-nucleotide polymorphisms (SNP) that are associated with disease development and/or higher disease activity are cytotoxic T lymphocyte-associated protein 4 (*CTLA4*), tumor necrosis factor (*TNF*), Fc receptor-like 3 (*FCRL3*), trypsin 1 (*PRSS1*), and cystic fibrosis transmembrane conductance regulator (*CFTR*) [8–12]. More comprehensive analyses such as genome-wide association studies (GWASs) are needed in order to more fully understand the genetic risks of this condition.

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Autoimmunity as an Initiator of Inflammation

Autoimmunity is currently suspected to be the most possible etiology of IgG4-RD including IgG4-SC and IgG4-AIP [13, 14]. Clinical findings showing that antinuclear antibodies are present in ~40% of patients with IgG4-RD suggest the involvement of autoimmunity in disease initiation or progression [8, 9]. Patients also frequently have autoantibodies against carbonic anhydrase II (CA-II), lactoferrin, pancreatic secretory trypsin inhibitor, and/or trypsinogens [8, 10]. Although the presence of these autoantibodies may explain predominantly lobular injury and other organ involvement (some of these enzymes are also expressed in other organs) in IgG4-RD, some may simply be secondary to extensive acinar destruction. None of the autoantibodies identified in patients with IgG4-RD have been proven to be of the IgG4 subtype.

In a recent study, circulating IgG1 and IgG4 isolated from patients with IgG4-AIP were subcutaneously injected into neonatal mice in order to elucidate the tissue reactivity of patient-derived immunoglobulins [11]. IgG1 and IgG4 both caused pancreatic injury, as evidenced by stromal edema, acinar necrosis, hemorrhage, and the infiltration of polymorphonuclear leukocytes, and histological changes were more extensive with IgG1. Interestingly, tissue destruction induced by IgG1 was suppressed by the simultaneous injection of patient IgG4, suggesting that IgG1 is the primary autoantibody against the pancreas, while patient IgG4 may exert inhibitory effects on pancreatic injury [11]. The similar anti-inflammatory induction of IgG4 was previously reported in allergic individuals treated with desensitization therapy [12].

Unlike classic autoimmune disorders, patients with IgG4-RD are older (median age, 67 years) and 80% are male. No disease-specific autoantibodies have been identified to date. Therefore, the autoimmune nature has not been fully proved yet. Other suspected pathogenetic processes include allergic reactions, a lymphoproliferative nature, and immune-complex deposition disease; however, no conclusive data is available for any of these possibilities.

Environmental Factors

Serum IgG4 concentrations are known to increase in subjects who have had chronic repeated exposure to antigens [15]. An example of this is that beekeepers show serum IgG4 elevation in the absence of IgE elevation. Given that occupational exposure to other antigens leads to the same phenotype, a European group suspected a possible role of work environment in disease development and examined the occupational history of patients with IgG4-SC and/or IgG4-AIP [16].

Of 25 patients with IgG4-RD in Amsterdam, 88% were blue-collar workers, whereas only 14% of those with primary sclerosing cholangitis (PSC) had a history of working in a blue-collar profession. This observation was validated by a separate cohort in Oxford, where blue-collar workers accounted for 61% of patients with IgG4-related pancreatocholangitis but only 22% of those with PSC [16]. Intensive and prolonged exposure to solvents, industrial dust, industrial oil, or polymers may play a role in the initiation of IgG4-RD in susceptible individuals. The causative factors may differ among patients, although the resultant immune reactions are similar. This hypothesis may also explain why IgG4-SC commonly develops in middle-aged men.

T Cells

Immunological features of IgG4-RD are summarized in Fig. 3.1. T-helper (Th) 2 lymphocytes and regulatory T cells (Tregs) are known to be upregulated in IgG4-SC [17, 18]. A caveat is that Th1 lymphocytes are not completely suppressed because the number of Th1 lymphocytes and expression of Th1 cytokines in IgG4-SC are similar to those in PSC. In contrast, Th2 cytokines such as IL-4, IL-5, and IL-13 are significantly overexpressed (Fig. 3.2) [17]. Th2-dominant immune reactions in IgG4-SC seem to be reasonable,

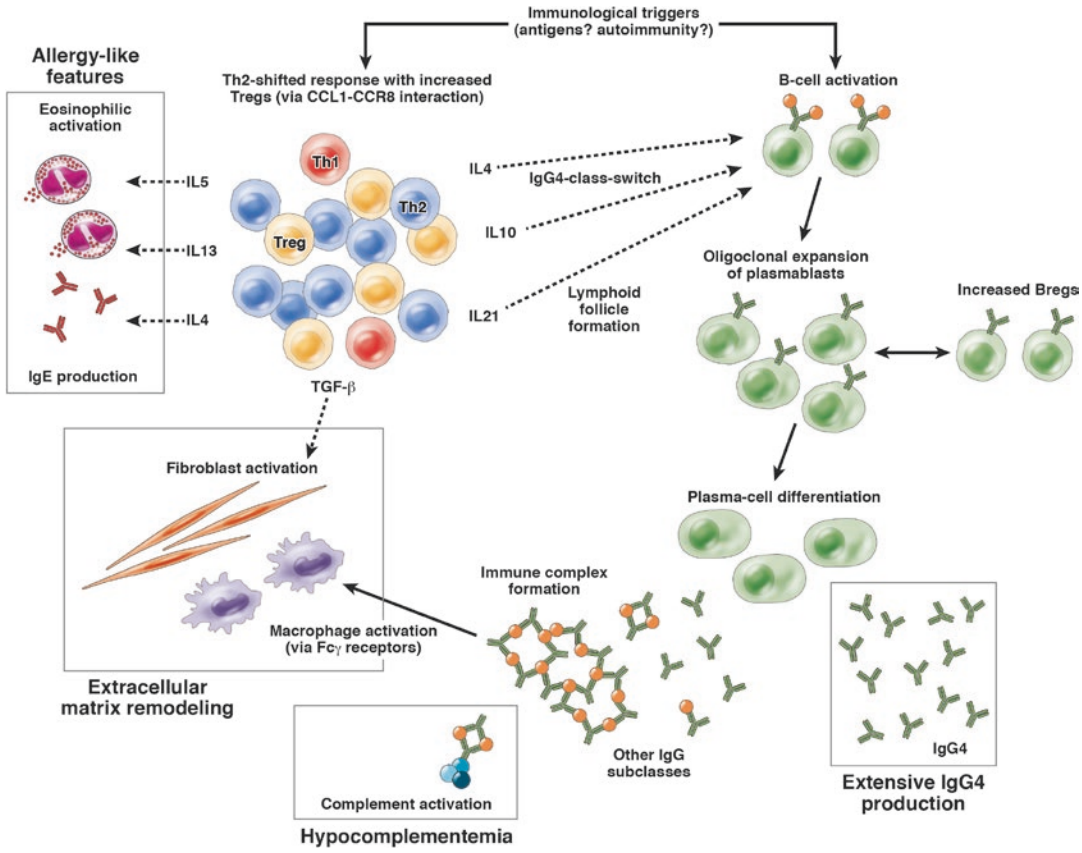

Fig. 3.1 Proposed immunological interactions in IgG4-SC and IgG4-AIP. (Copyright © 2015 AGA Institute. Part PA, Zen Y, Chari ST. Recent advances in autoimmune pancreatitis. 2015;149:39–51. Reprinted with permission from Elsevier Inc.)

because patients sometimes have serum eosinophilia and elevated IgE concentrations. Th2 cytokines produced in tissue may be involved in these systemic serological features [17, 18].

Tregs are also likely activated in IgG4-SC. This is another argument against the hypothesis that IgG4-SC is an autoimmune disease because the functions of this subset of immune-suppressive T cells are generally decreased in classic autoimmune disorders [19, 20]. Histologically, a large number of FOXP3+CD4+CD25+ Tregs are present in bile duct tissue with IgG4-SC, along with the overexpression of two regulatory cytokines (IL-10 and TGF-β) [17, 21]. IL-10 is suspected to participate in an IgG4 class switch in B cells. When IL-4 and IL-10 simultaneously act on B cells, the production of IgG4 is known to be selectively induced [22]. Therefore, Treg activation against the background of Th2-dominant immune reactions may provide a driving force toward an IgG4 class switch via IL-4 and IL-10. TGF-β is a strong fibrogenic cytokine, likely contributing to fibrosis in this sclerosing condition [18].

A more recent study also demonstrated that the number of circulating Tfh2 cells was increased in patients with IgG4-RD, and these numbers correlated with plasmablast counts and the serum levels of IL-4 and IgG4 [23, 24]. Since Tfh cells are a distinct subset of CD4+ T cells that play critical roles in germinal center formation and expedite B-cell and plasma cell differentiation, Thf2 cells may play a crucial role in T-cell-B-cell interactions in IgG4-RD [25]. IL-21 is the most important cytokine produced by Tfh2 cells for

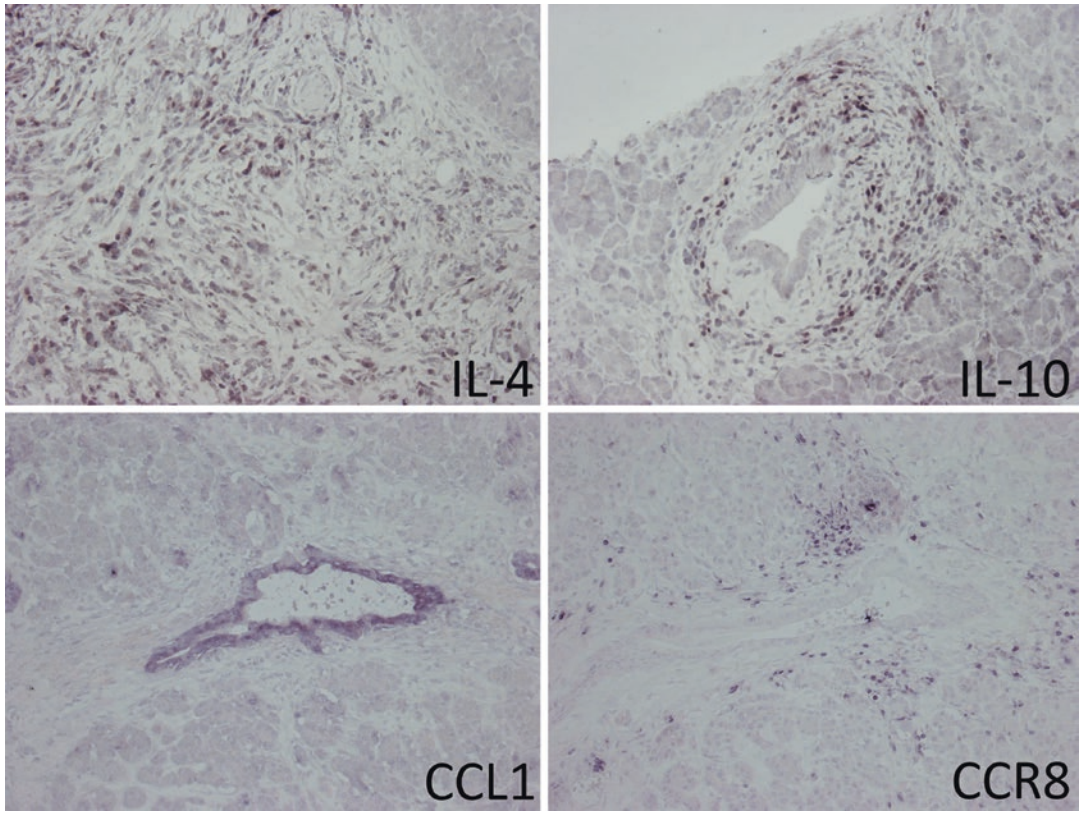

Fig. 3.2 Immunological factors expressed in IgG4-SC and IgG4-AIP (in situ hybridization). Lymphocytes expressing IL-4 or IL-10 are observed. The pancreatic duct positive for CCL1 is surrounded by CCR8+ lymphocytes. (Upper panels: Copyright © 2007 American Association for the Study of Liver Diseases. Zen Y, Fujii T, Harada K, et al. Th2 and regulatory immune reactions are increased in immunoglobin G4-related sclerosing pancreatitis and cholangitis. Hepatology 2007;45:1538–46. Lower panels: Copyright © 2013 European Association for the Study of the Liver. Zen Y, Liberal R, Nakanuma Y, et al. Possible involvement of CCL1-CCR8 interaction in lymphocytic recruitment in IgG4-related sclerosing cholangitis. J Hepatol 2013;59:1059–64)

the development of germinal center, and it was proven to be upregulated in IgG4-related sialodacryoadenitis [26]. However, it is important to note that germinal center formation is less common in IgG4-SC than in IgG4-related sialodacryoadenitis [27].

Chemokines and Chemokine Receptors

Although the massive inflammatory infiltrate is the histologic hallmark of this condition, the roles of chemotactic factors in the immunopathology are poorly understood, with only less than a dozen chemotactic factors known to be upregulated (e.g., CXCL13, CCL18, and CCR4) [28, 29]. A critical question is which chemotactic factors are involved in creating a milieu rich in Th2 and Tregs. The expression of Th2 chemokines and their receptors were examined, and CCL1 and CCR8 appeared to be upregulated in IgG4-SC [30]. These two molecules seem to be important because 50% of Th2 lymphocytes and 60% of FOXP3+ Tregs express CCR8 [31]. CCL1 is expressed in the ductal and glandular epithelia in IgG4-SC. CCR8-positive lymphocytes are also present around the bile ducts and peribiliary glands, suggesting CCL1-CCR8 interactions operating in these particular microscopic foci (Fig. 3.2) [31]. Another source of CCL1 is endothelial cells. The endothelium involved in

obliterative phlebitis is positive for CCL1 and is infiltrated by CCR8-positive lymphocytes, suggesting that CCL1-CCR8 interactions may also cause obliterative phlebitis [31].

It currently remains unclear why the biliary epithelium is intact despite the expression of CCL1. Although there are CCR8-positive Th2 lymphocytes and Tregs around the ducts, intraepithelial lymphocytes are rare. One possible explanation is that Th2 lymphocytes and Tregs may not be strong enough to infiltrate the basement membrane. A previous study demonstrated that the bile duct epithelium is damaged at the molecular level despite its unremarkable morphological appearance. The biliary epithelium in IgG4-SC has impaired barrier function because of the abnormal expression of cell adhesion molecules such as claudins, which are supposedly induced by a direct interaction between Th2 cytokines and their receptors expressed on cholangiocytes [32].

B Cells

Recent studies have examined the B-cell aspects of IgG4-RD, and their findings have been reinforced by the clinical observation that B-cell depletion therapy with anti-CD20 antibodies is effective in patients with IgG4-RD [33, 34]. Two subsets of B cells (regulatory B cells [Bregs] and plasmablasts) are upregulated in IgG4-RD. Similar to Tregs, a subset of Bregs may be activated under these conditions [35]. A recent study suggested that IL-10-producing Bregs have a strong capacity to produce IgG4 [36]; however, their involvement in this particular condition remains to be examined. Molecular studies using a next-generation sequencing protocol have identified the oligoclonal expansion of IgG4-switched B cells and CD19+CD20−CD27+CD38+ plasmablasts in IgG4-RD [21, 37]. Circulating plasmablasts are largely IgG4-positive and have undergone extensive somatic hypermutation [37, 38]. Recombinant IgG4 molecules derived from the most dominant IgG4-positive plasmablasts in a patient with IgG4-RD were also shown to react with human cells [37].

IgG4 Molecules

IgG4 is a key molecule in immunological reactions in IgG4-SC because massive infiltration by IgG4-positive plasma cells is a consistent histological hallmark of this condition. However, it remains unclear whether IgG4 molecules are induced in a pro- or anti-inflammatory manner. When IgG4 elevations were discovered in patients with IgG4-AIP, many investigators suspected that IgG4 functioned as a tissue-destructive antibody. However, IgG4-type autoantibodies have never been confirmed in patients with IgG4-RD. A general view is that IgG4 is a noninflammatory antibody because of its relative inability to fix complement and its poor capacity to bind to Fc receptors [15, 39]. Another unique feature of IgG4 molecules is "Fab-arm exchange," a process in which a pair of heavy and light chains of an IgG4 antibody is exchanged with those derived from another IgG4 [40]. Due to this structural change, IgG4 molecules become asymmetric, eventually lose their antigen cross-linking ability, behave as monovalent antibodies, and become incapable of forming large immune complexes [4]. Due to the anti-inflammatory properties of IgG4, many investigators currently suspect that IgG4 may be secondarily induced to dampen extensive immune reactions in IgG4-RD.

Activated Immunological Signal Pathways

A recent global proteomic study on IgG4-SC identified activated signal cascades in affected tissue [41]. Protein profiles in the frozen bile duct tissue of IgG4-SC were compared with those of PSC. To the best of our knowledge, this was the first non-biased global tissue examination of IgG4-SC. A robust proteomic approach with phosphopeptide enrichment methods identified 23,373 peptides and 4870 proteins, including 4801 phosphopeptides and 1121 phosphoproteins [41].

The expression profiles of phosphopeptides discriminated IgG4-SC from PSC better than those of non-phosphopeptides, suggesting that

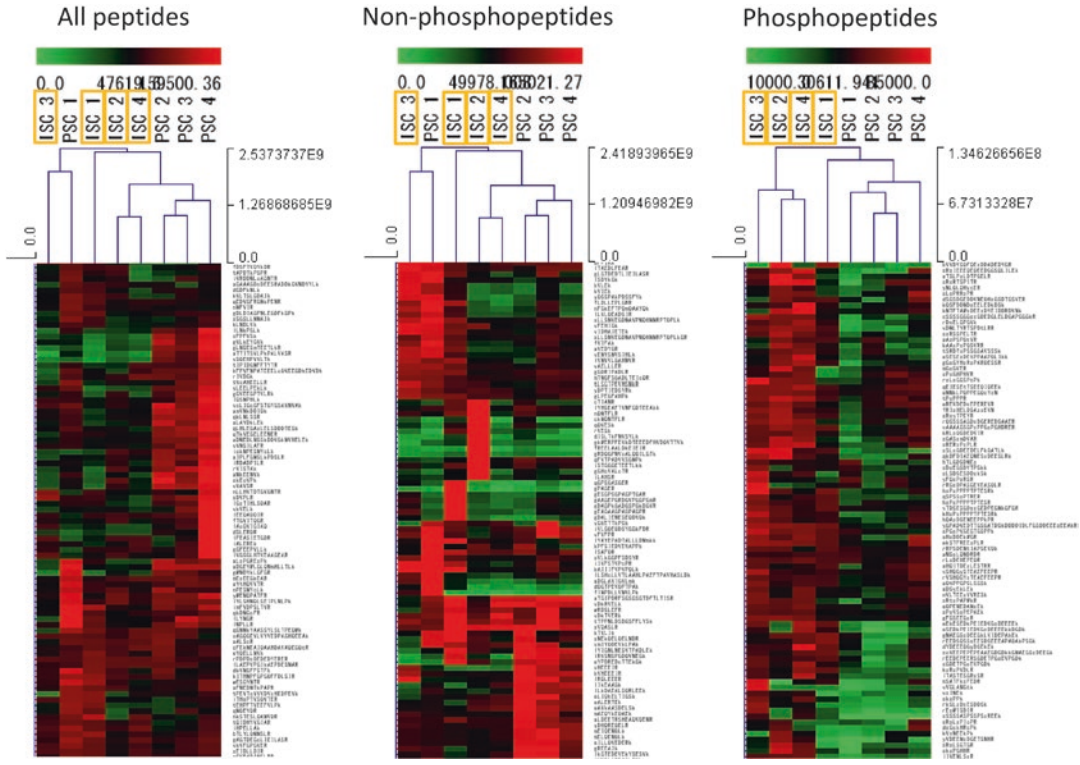

Fig. 3.3 Protein expression profiles in frozen bile duct samples of IgG4-SC. Proteins extracted from frozen bile duct samples of IgG4-SC (ISC) and PSC cases (n = 4 each) were examined in a global non-biased manner. Clustering analysis of IgG4-SC and PSC cases was performed based on the expression profiles of non-phosphopeptides, phosphopeptides, or both. The analysis based on phosphopeptides only showed better separation than the other two. Each row represents individual peptides identified by the proteomic analysis. Since whole heat maps are very long, only representative areas are shown. (Copyright © 2015 John Wiley & Sons Ltd. Reprinted from Zen Y, Britton D, Mitra V, et al. A global proteomic study identifies distinct pathological features of IgG4-related and primary sclerosing cholangitis. Histopathology 2016;68:796–809)

the phosphorylation status of proteins better characterizes these conditions than their expression levels (Fig. 3.3) [41]. In the pathway analysis based on strongly expressed or highly phosphorylated proteins, IgG4-SC was found to have 11 more activated signal cascades including three immunological pathways than PSC. Interestingly, the three immune cascades were all B-cell- or immunoglobulin-related. The most significantly modulated immunological pathway was Fcγ receptor-mediated phagocytosis (Fig. 3.4) [41]. This is a signal cascade that is triggered by the interaction between IgG molecules and Fcγ receptors on the cell membrane. It is important to note here again that IgG4 has a poor capacity to bind to Fc receptors [15]. Therefore, it remains unclear whether IgG4 or other IgG subclasses activate this signaling pathway under this particular condition.

The other two activated cascades were the B-cell receptor signaling pathway and Fcε receptor I signaling pathway (Fig. 3.4) [41]. The former pathway is activated by the interaction between B-cell receptors on B cells and antigens and causes B-cell activation. The latter is an IgE-mediated signal leading to activation of eosinophils and Th2 lymphocytes. In line with this result, a recent study also suggested activated interaction between IgE and mast cells in tissue of IgG4-SC and IgG4-AIP [42]. Since no pathways directly related to T cells appeared to be significantly modulated between the two condi-

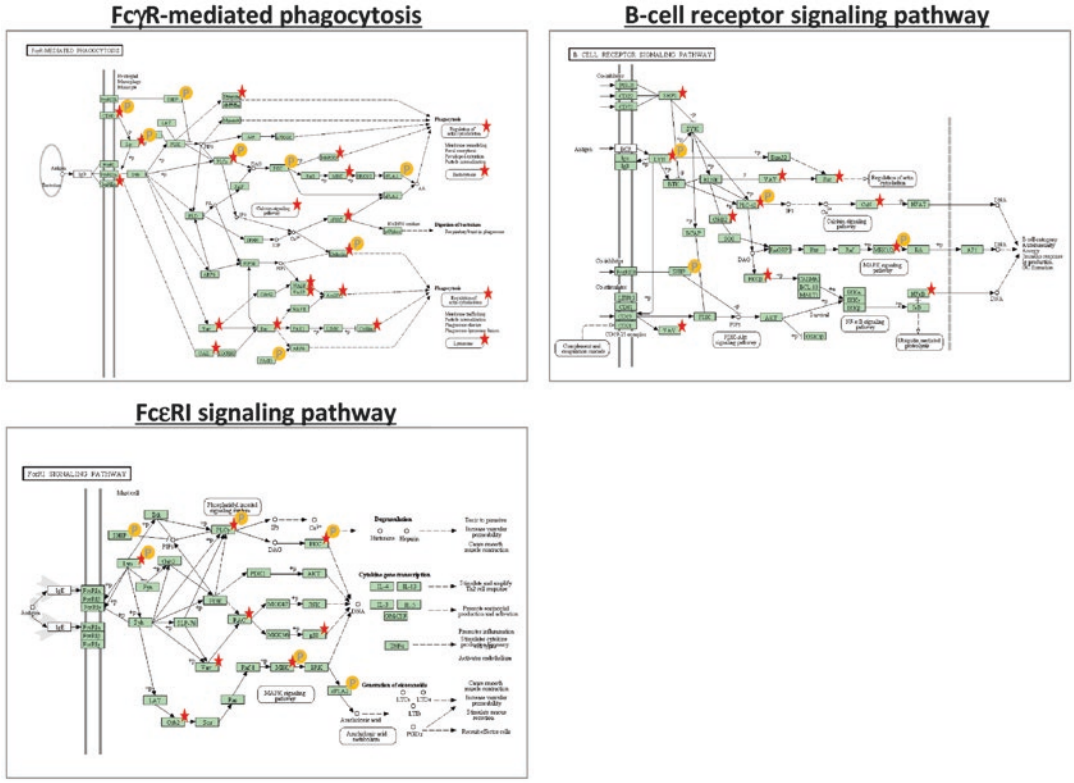

Fig. 3.4 Activated immunological signaling pathways in IgG4-SC. Three immunological signaling pathways were determined to be more activated in IgG4-SC than in PSC by the pathway analysis. Many proteins involved in these cascades were more abundant (marked with red stars) or more phosphorylated (marked with "P" marks) in IgG4-SC. (Copyright © 2015 John Wiley & Sons Ltd. Reprinted from Zen Y, Britton D, Mitra V, et al. A global proteomic study identifies distinct pathological features of IgG4-related and primary sclerosing cholangitis. Histopathology 2016;68:796–809)

tions, B-cell immune responses may better discriminate the immunological features of IgG4-SC and PSC. This may also explain why rituximab works well in patients with IgG4-SC.

Macrophage Activation

The abovementioned global proteomic study also identified individual proteins that are significantly abundant in either condition [41]. Two highly overexpressed molecules in IgG4-SC were FYN-binding protein and allograft inflammatory factor-1. On immunostaining for these markers, FYN-binding protein was expressed in macrophages and T lymphocytes, while allograft inflammatory factor-1 was positive in macrophages (Fig. 3.5) [41]. The co-expression of these two proteins in macrophages suggests the potential involvement of macrophages in the pathogenesis of IgG4-SC. FYN-binding protein is usually expressed in T cells and myeloid cells and is possibly involved in the positive regulation of T-cell activation as well as IL-2 production. The role of FYN-binding protein in macrophages is largely unknown, but its involvement in their phagocytotic process has been suggested. Allograft inflammatory factor-1, originally cloned from a rat heart allograft under chronic rejection, is known to be upregulated during the activation of macrophages. The expression of allograft inflammatory factor-1 enhances the production of cytokines such as IL-6, IL-10, and IL-12 and augments the phagocytotic activity of macrophages.

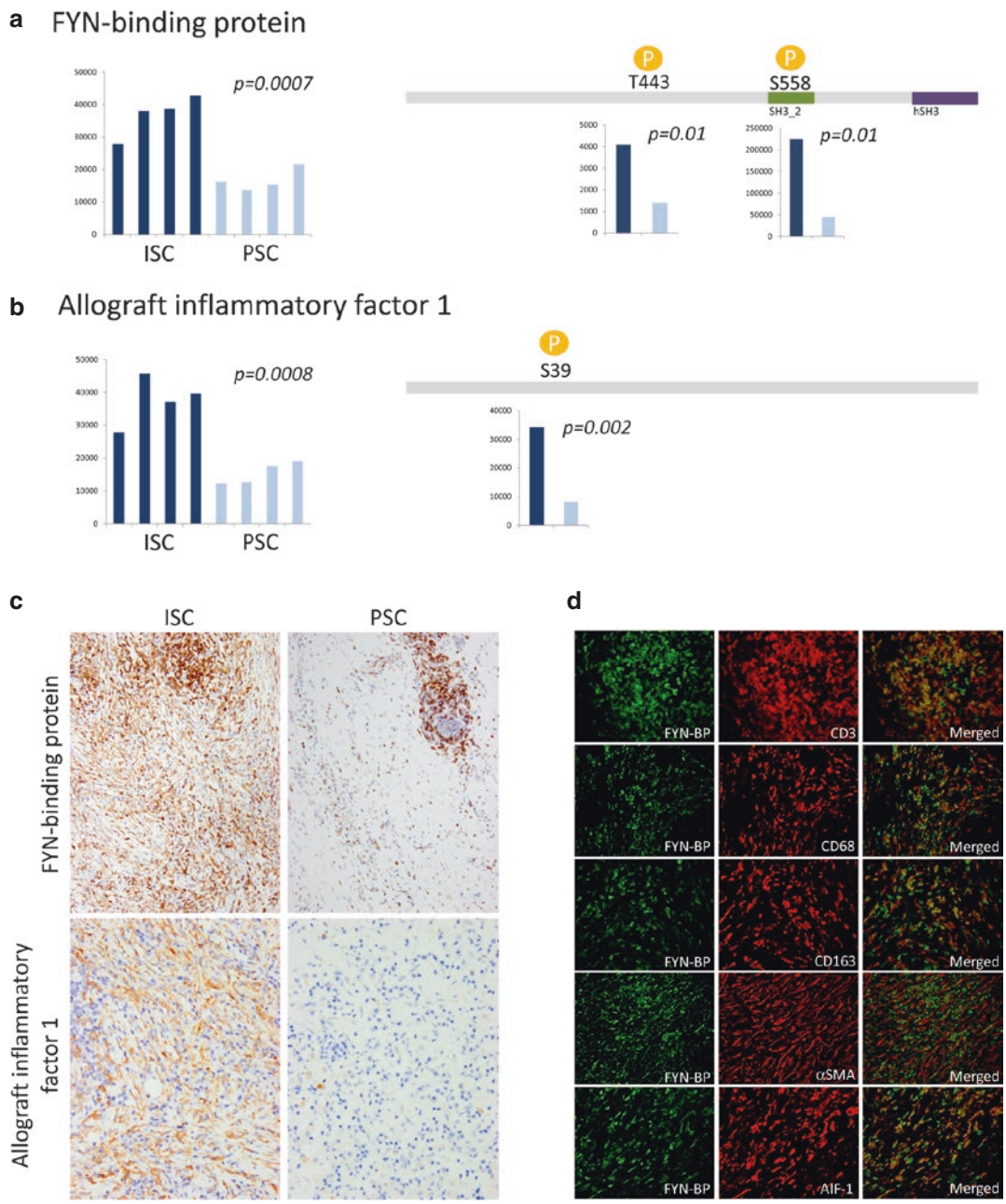

Fig. 3.5 Overexpressions of FYN-binding protein and allograft inflammatory factor-1 in IgG4-SC. (**a**, **b**) In the proteomic study, expressions of FYN-binding protein and allograft inflammatory factor-1 were significantly higher in IgG4-SC (ISC) than in PSC. In addition, three phosphorylation sites in these proteins were significantly more phosphorylated in IgG4-SC. (**c**) On immunostaining, FYN-binding protein was diffusely expressed in stromal cells in addition to lymphocytes in IgG4-SC, while its expression was restricted to lymphocytes in PSC. The expression of allograft inflammatory factor-1 was also more diffuse in IgG4-SC. (**d**) Dual fluorescent immunostaining showed that some of the cells expressing FYN-binding protein (FYN-BP) were positive for CD3 (T lymphocytes), while other cells expressed CD68 and CD163, in keeping with M2-type macrophages. No expression of αSMA was noted in FYN-BP+ cells. Some macrophages were double positive for FYN-binding protein and allograft inflammatory factor-1 (AIF-1). (Copyright © 2015 John Wiley & Sons Ltd. Reprinted from Zen Y, Britton D, Mitra V, et al. A global proteomic study identifies distinct pathological features of IgG4-related and primary sclerosing cholangitis. Histopathology 2016;68:796–809)

These findings are in keeping with the result of pathway analysis that Fcγ receptor-mediated phagocytosis in macrophages was determined to be an activated signaling cascade in IgG4-SC [41]. Another interesting aspect is that macrophages expressing FYN-binding protein and allograft inflammatory factor-1 were positive for CD163, suggesting the M2-type phenotype. A recent study reported a possible role of M2 macrophages in the fibrosing process in other organ manifestations of IgG4-RD [43]. To summarize, macrophages, particularly M2 type, are likely activated with enhanced phagocytotic function probably due to the IgG-Fcγ receptor interaction and may be involved in an orchestrated immune reaction by regulating cytokine production in IgG4-SC.

Future Perspectives

In the last decade, our knowledge of molecular features of IgG4-SC has expanded, particularly in terms of T-cell activation, T-cell-B-cell interaction, cytokine production, and following activated signal cascades (Fig. 3.5). However, many important questions remain unanswered. One example is the exact role of IgG4 in the pathogenesis of IgG4-SC. Another question is whether IgG4-SC is truly an autoimmune disease. Future studies focusing on these aspects will be required to fully understand the biology of this emerging form of cholangiopathy.

Conflict of Interest None to declare.

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Pathology

4

Kenji Notohara

Introduction

Primary sclerosing cholangitis (PSC) has been known since the early twentieth century. It had been considered rare until the 1970s, when the number of patients started to increase due to the development of endoscopic retrograde cholangiopancreatography. Although the clinicopathological features of PSC reported by different groups were consistent, there was a subset of unique PSC cases which occurred in the setting of systemic sclerosing diseases (multifocal fibrosclerosis). For example, Bartholomew and colleagues [1] reported PSC in a patient with Riedel's thyroiditis and retroperitoneal fibrosis. Nowadays, many of the cases reported as multifocal fibrosclerosis are presumed to be IgG4-related disease (IgG4-RD), and PSC in this particular setting might represent IgG4-related sclerosing cholangitis (IgG4-SC). Thus, IgG4-SC was likely included among cases of PSC in the old literature.

Unique histological features of IgG4-SC were reported by Kawaguchi and colleagues [2]. They reported two cases with lymphoplasmacytic sclerosing pancreatitis (LPSP), which is now considered equivalent to autoimmune pancreatitis (AIP). They also found that the bile duct wall was thickened by inflammation that was histologically similar to LPSP. They realized that the bile duct lesion was atypical for PSC and called it a variant of PSC. We also confirmed their findings with a larger number of resected specimens of AIP/LPSP [3]. Zen and colleagues later analyzed similar cases and clarified that there were numerous IgG4-positive cells in the lesions and that IgG4-SC could occur in the absence of AIP [4]. From the clinical standpoint, Nakazawa and colleagues [5, 6] described IgG4-SC (they coined the term "sclerosing cholangitis with AIP" in their reports) as unique and distinct from PSC because of the different features of the cholangiogram, increased level of serum IgG4, absence of inflammatory bowel disease, effective corticosteroid treatment, and excellent prognosis.

Based on these pathological and clinical findings, IgG4-SC was established as an entity. We have learned from previous studies that IgG4-SC can be diagnosed through histological examination, but the diagnosis must be clinically consistent.

Macroscopic Features

The bile ducts are classified into large and small intrahepatic bile ducts. The large bile ducts include the extrahepatic bile duct through the third generation of intrahepatic bile ducts.

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The small intrahepatic bile ducts are subclassified into septal (>100 μm) and interlobular ducts (<100 μm) depending on their caliber. Each biliary disease is known to involve different categories of bile ducts.

Because IgG4-SC is hard to distinguish from biliary cancers clinically, resections may be carried out with a clinical suspicion of cancer. Thus, pathologists may have a chance to examine the entire lesion in IgG4-SC. IgG4-SC commonly involves the large bile ducts. The walls of the involved ducts are markedly thickened with inflammation. The ducts are stenotic, but the surface is smooth and glossy because the lesions lack epithelial injury, ulceration, or epithelial regeneration that may result in irregularity of the mucosal surface. These findings are different from those of biliary cancers and PSC. The wall thickening can be found beyond the stenosis of the bile ducts, although this is not the case for biliary cancers.

Among the large bile ducts, the lower extrahepatic bile duct and hepatic hilum are commonly involved. The former lesion is common in patients with AIP and is rarely found without AIP. In fact, more than 90% of IgG4-SC cases occur in patients with AIP, and therefore the lower extrahepatic bile duct is the most common location of IgG4-SC. Pathologists can observe the lower bile duct lesions when they examine pancreatoduodenectomy specimens of AIP. In contrast, involvement of IgG4-SC in the hepatic hilum often occurs in patients without AIP. From the clinical standpoint, IgG4-SC in the hepatic hilum is very difficult to distinguish from biliary cancers (Klatskin tumor), notably in cases without AIP. IgG4-SC often extends to the surrounding connective tissue in the hepatic hilum, and if this finding becomes conspicuous, such lesions are called inflammatory pseudotumors [7]. Importantly, IgG4-SC may present multifocal lesions. Such cases are more easily diagnosed by clinicians as IgG4-SC rather than biliary cancers, and pathologists do not receive resected specimens. In cases with multifocal stenosis in the intrahepatic bile duct, distinguishing IgG4-SC from PSC becomes important.

General Histological Features of IgG4-RD

Before explaining in detail the histological features of IgG4-SC, I will discuss the general histological features of IgG4-RD. IgG4-RD occurring in different organs histologically shares some features, although the frequency and distribution of these features may differ depending on the organ.

IgG4-RD comprises dense inflammatory cell infiltration with fibrosis that causes wall thickening, mass formation, or diffuse organomegaly. Thus, the clinical presentation is similar to that of neoplastic diseases, such as carcinomas and malignant lymphomas. Diffuse lymphoplasmacytic infiltration is usually marked; notably, plasma cells are present diffusely and conspicuously. Lymphoid follicles and eosinophils are often admixed and may be numerous in occasional cases. In general, neutrophils are absent, but there are some exceptions, i.e., neutrophils in the bronchi in IgG4-related lung disease and neutrophils in the lobules in type 1 AIP, although neutrophils in such examples can be a secondary phenomenon rather than a specific finding of IgG4-RD.

Storiform fibrosis is one of the histological features that characterize IgG4-RD. Storiform fibrosis is a swirling pattern of inflammation that is composed of small spindle-shaped cells, inflammatory cells (mainly lymphocytes and plasma cells as explained earlier) and various amounts of fibrosis (Fig. 4.1). Despite the use of the term “fibrosis,” storiform fibrosis may be cellular with scarce fibrosis (Fig. 4.1a). Cellular lesions of storiform fibrosis seem to gradually transition into true fibrosis (Fig. 4.1b) and finally give rise to complete fibrosis (Fig. 4.1c). This is similar to the ordinal granulation tissue giving rise to fibrosis with time. Although the definition of storiform fibrosis may differ among pathologists, in my opinion, identifying cellular and transitional (between cellular and fibrosing) types is important to making a diagnosis of IgG4-RD, and there are mimickers that resemble the pauci-cellular fibrosing type of storiform

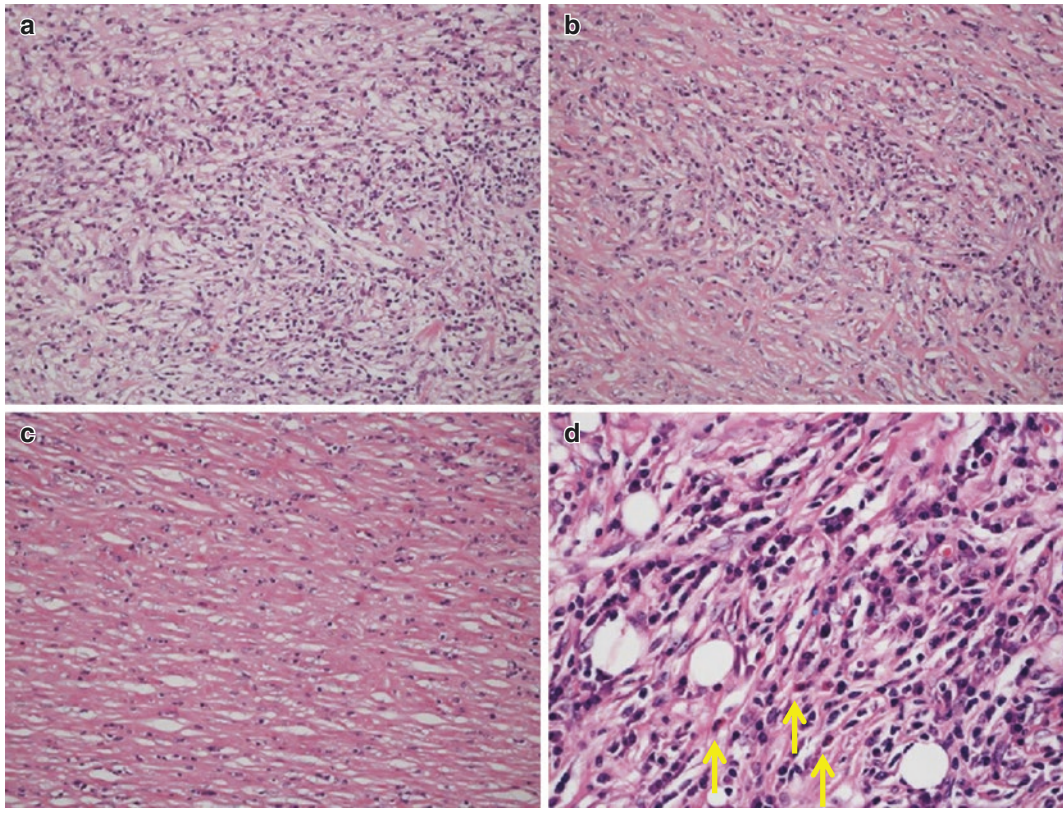

Fig. 4.1 Storiform fibrosis in autoimmune pancreatitis. Storiform fibrosis may be cellular (**a**), transitional between cellular and fibrosing (**b**), or fibrosing (**c**). The cellular and transitional forms (**b**) are diagnostically significant. Inflammatory cells are composed of lymphocytes and plasma cells, and eosinophils (arrows) are often intermingled (**d**)

fibrosis. The frequency of storiform fibrosis is different depending on the organ; it is common in the abdominal lesions of IgG4-RD, such as AIP, retroperitoneal fibrosis, interstitial nephritis, and periaortitis. In contrast, storiform fibrosis is rare in the orbit and lymph nodes and may be mild in the salivary glands. The reason for such different prevalences of storiform fibrosis is unknown.

Obliterative phlebitis is another important finding in IgG4-RD. It is a venous obliteration by the characteristic inflammatory lesion seen in IgG4-RD (Fig. 4.2a, b). Typical obliterative phlebitis is observed in the small veins (venules), but larger muscular veins up to the level of the splenic and even portal veins may also be involved. In cases with large vein involvement, however, complete obstruction of the lumen is rare, and a portion of the venous wall is involved in the inflammation. In a similarity to storiform fibrosis, obliterative phlebitis is also cellular with inflammatory cells, and storiform fibrosis may also be observed in the obliterated veins. Obliterative phlebitis could be pauci-cellular and fibrotic, notably with the remission of the inflammation. Complete fibrous obliteration of veins, however, can be observed in various destructive diseases, for example, pancreatic cancers and chronic pancreatitis in the pancreas (Fig. 4.2c, d) [8]. Thus, similar to storiform fibrosis, identifying cellular and transitional types of obliterative phlebitis is significant for diagnosing IgG4-RD. It is noteworthy to mention that fibrous obliterated veins in cases with non-IgG4-related destructive diseases can usually be identified only with elastic stains,

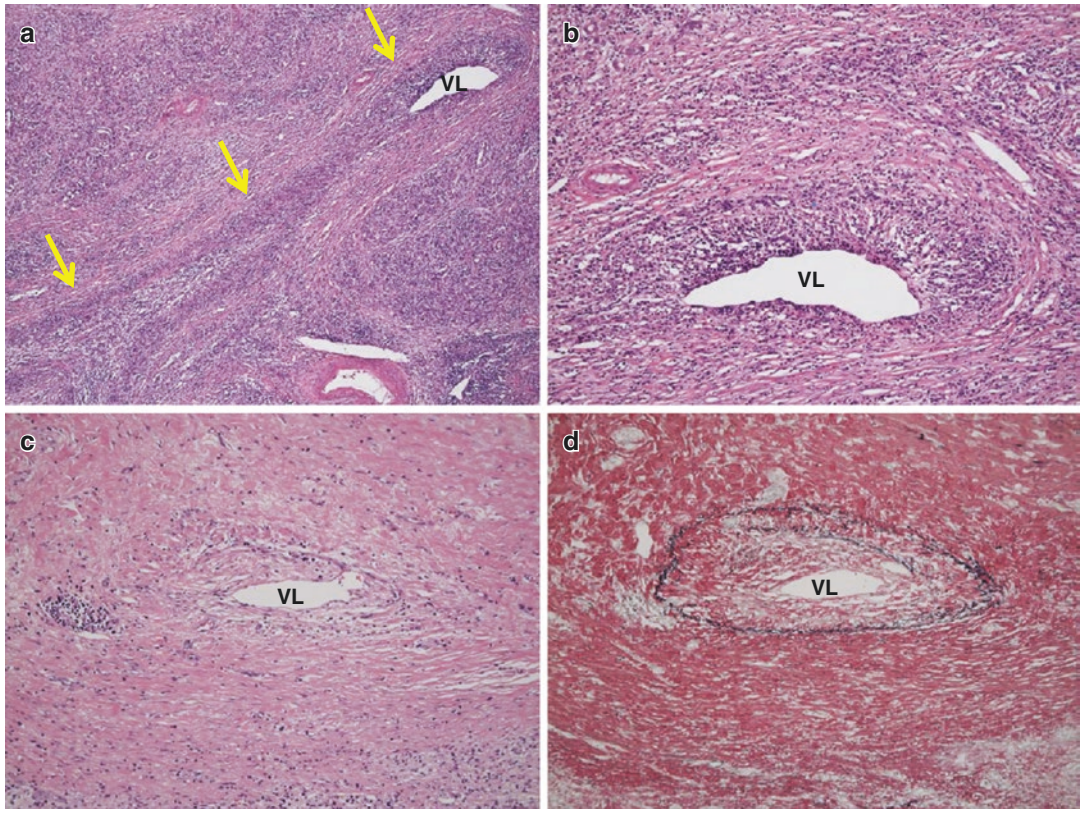

Fig. 4.2 Obliterative phlebitis in autoimmune pancreatitis (**a**, **b**) in comparison with fibrous venous obliteration found in chronic pancreatitis (**c**, **d**). A longitudinal vein (arrows) is obliterated by the inflammation (**a**). Venous contour is evident even with hematoxylin-eosin stain. Note that the inflammation observed within and around the vein is histologically similar (**b**). A vein is obliterated by fibrous tissue in **c** and **d**. In contrast to **a** and **b**, venous obliteration is not evident with hematoxylin-eosin stain alone. *VL* venous lumen

such as Verhoeff-van Gieson stain (Fig. 4.2c, d). In contrast, cellular and transitional types of obliterative phlebitis in IgG4-RD can be identified even on hematoxylin-eosin-stained slides, because the contour of the veins is still well preserved (Fig. 4.2a, b). Thus, it is dangerous to depend only on elastic stains to identify obliterative phlebitis.

The distribution of the inflammation is also unique and peculiar in IgG4-RD, and margins of anatomical structures are often involved. For examples, the inflammatory cells surround the pancreatic ducts without involving the epithelium (Fig. 4.3a). In AIP, the pancreas itself is surrounded by the thick fibroinflammatory lesion, which corresponds to a radiological feature called a capsule-like rim (Fig. 4.3b). Retroperitoneal fibrosis is characterized by inflammation around the abdominal aorta or ureter. In the stroma of various sites, microscopic findings of periarteritis (Fig. 4.3c) and perineuritis (Fig. 4.3d) are commonly identified. Importantly, the parenchyma of these affected structures is often intact or minimally damaged, and this may explain why the tissue damage is mild in IgG4-RD in comparison with the severe inflammatory infiltration.

Immunohistochemically, numerous IgG4-positive cells are identified in IgG4-RD. This feature will be discussed in the following section.

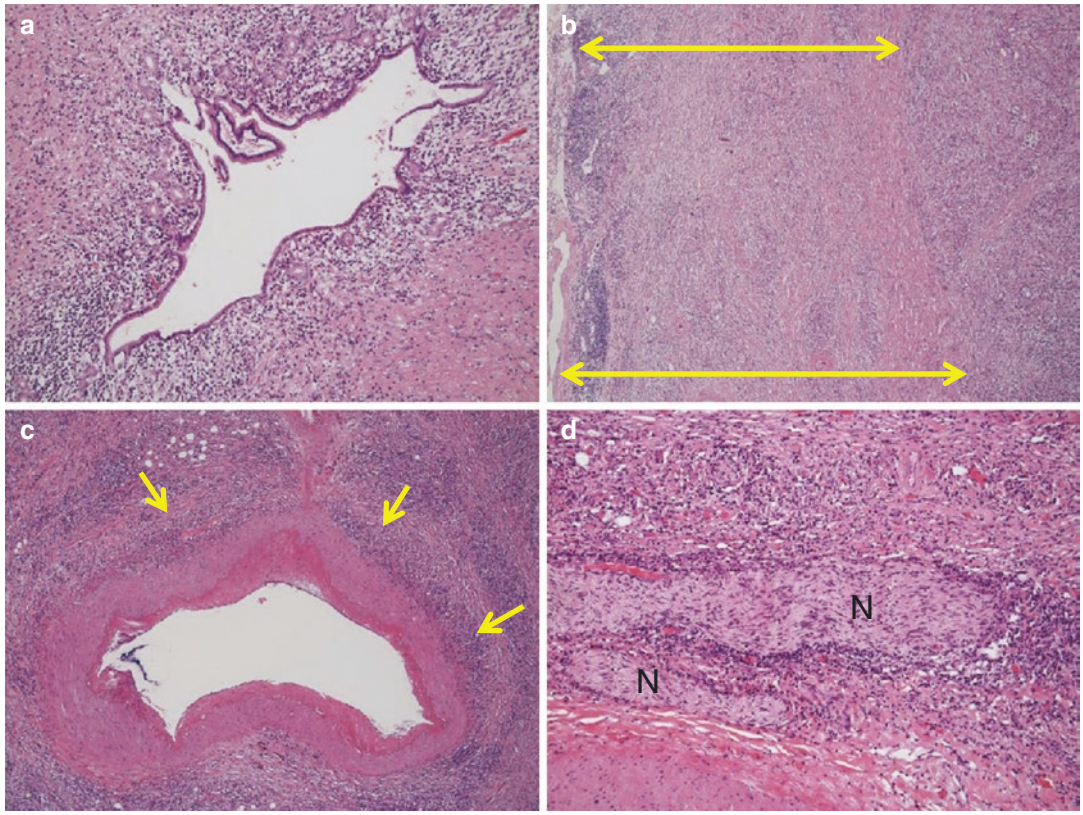

Fig. 4.3 Inflammatory distribution at the margins of various anatomical structures in autoimmune pancreatitis. Periductal involvement of the inflammation without causing epithelial changes (**a**). A thick collar of the inflammation (two-direction arrows) at the margin of the pancreas (**b**). The right side of the picture is the pancreas parenchyma. Periarteritis (**c**) in which the external elastic lamina is blurred by the inflammation (arrows). Perineuritis (**d**) with dense inflammatory cell infiltration around the nerves. *N* nerve fiber

Histological Findings of IgG4-SC

The inflammation in IgG4-SC is observed around the bile duct epithelium with the epithelium left intact, which is a typical example of the marginal distribution of IgG4-RD [4, 9, 10]. There is no damage, inflammatory infiltration (small numbers of lymphocytes may be present, but neutrophils are absent), or regenerative changes in the bile duct epithelium. In the resected specimens with IgG4-SC, neutrophilic infiltration and/or erosion are often found on the surface, but this is due to a stent insertion for obstructive jaundice before the operation. Transmural inflammation with fibrosis that gives rise to wall thickening is the typical finding in the bile ducts (Fig. 4.4a). Such lesions seem like a thick wall of the bile duct. Typical storiform fibrosis with infiltration of lymphocytes, plasma cells, and often eosinophils is observed (Fig. 4.4b, c). In some cases, however, a band composed of simple inflammatory cell infiltration without forming storiform fibrosis may be found just beneath the bile duct epithelium and/or around the peribiliary glands (Fig. 4.4d).

Lesions of IgG4-SC often involve the connective tissue that surrounds the bile ducts. This finding is usually faint in the extrahepatic bile duct, but it is prominent in the hepatic hilum. In the

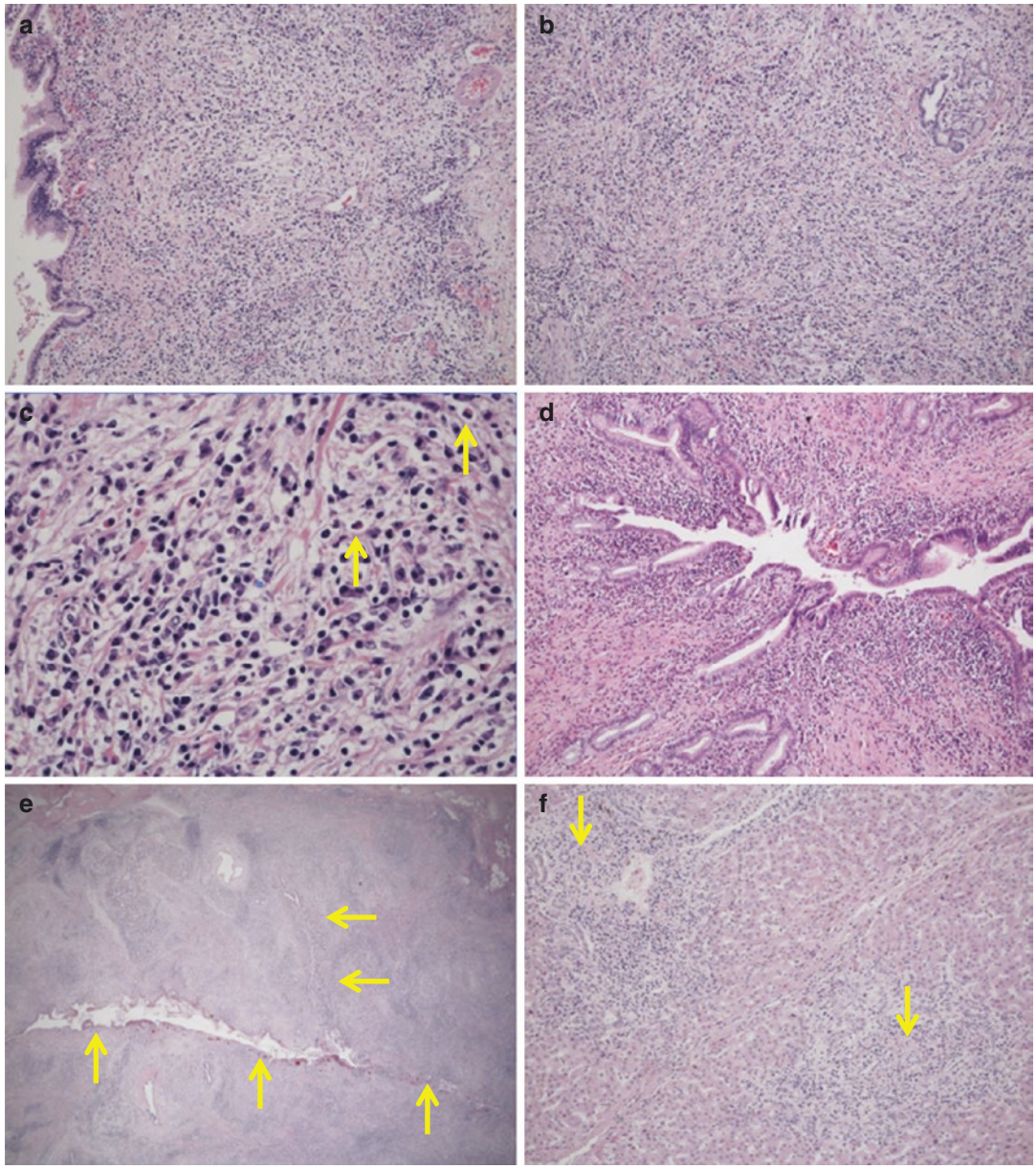

Fig. 4.4 IgG4-related sclerosing cholangitis. Typical collar-like inflammation of the large bile duct (**a**). Note that the bile duct epithelium is intact (left). In such lesions, storiform fibrosis is usually evident in the bile duct wall (**b**). Inflammatory cells are a mixture of lymphocytes, plasma cells, and eosinophils (arrows) (**c**). The inflammation sometimes consists of simple lymphoplasmacytic infiltration without storiform fibrosis that is found just below the epithelium (**d**). The typical inflammation around the bile ducts (arrows) extends diffusely into the surrounding connective tissue (**e**). The inflammation also extends to the periphery along the portal tracts, where lymphoplasmacytic infiltration is observed (**f**). Interlobular bile ducts are intact (arrows), although ductular proliferation is observed at the periphery of the portal tracts as a result of the biliary stricture

hepatic hilum, the bile duct lesions may expand diffusely into the surrounding loose connective tissue (Fig. 4.4e). The portal vein branches and peripheral nerves can also be involved in the inflammation, and the former gives rise to the obliterative phlebitis. The inflammation can also

extend into the periphery along the portal tracts (Fig. 4.4f), where dense lymphoplasmacytic infiltration with numerous IgG4-positive cells can be observed without bile duct lesions. Ductular proliferation is often prominent in the peripheral portal tracts due to the obstructive jaundice.

The inflammatory expansion in the soft tissue around the bile duct may be so eminent in some cases that it appears as a mass; such lesions are called IgG4-related inflammatory pseudotumors [7]. The histological findings of inflammatory pseudotumor are typical for IgG4-RD, consisting of dense lymphoplasmacytic infiltration, storiform fibrosis, obliterative phlebitis, and numerous IgG4-positive cells. Because IgG4-related inflammatory pseudotumors are almost always associated with IgG4-SC in the hepatic hilum, I regard this lesion as IgG4-SC with prominent soft tissue involvement. It is important to emphasize that inflammatory pseudotumors are not always IgG4-related; the fibrohistiocytic type, which Zen and colleagues reported [7], has different clinicopathological features and should not be confused with IgG4-RD.

IgG4 Immunostaining

An increase of IgG4-positive cells is a characteristic histological feature of IgG4-RD and is also evident in IgG4-SC (Fig. 4.5). For diagnosing IgG4-SC, the requisite number of IgG4-positive cells in a high-power field (HPF) is more than 50 in the resected tissues and more than 10 in the biopsied samples [11]. However, it is important to keep in mind that such numbers are not specific to IgG4-SC and can be observed in other biliary diseases, such as biliary cancers [12], PSC [13, 14], and cholelithiasis. In this respect, diffuse distribution of IgG4-positive cells and an increase in the IgG4/IgG-positive cell ratio (>40%) are important; usually both are observed in IgG4-SC but not in other diseases. According to the consensus statement on the pathological diagnosis of IgG4-RD, IgG4-positive cells and the IgG4/IgG-positive cell ratio are recommended to be evaluated in three foci with the most abundant IgG4-positive cells in each case.

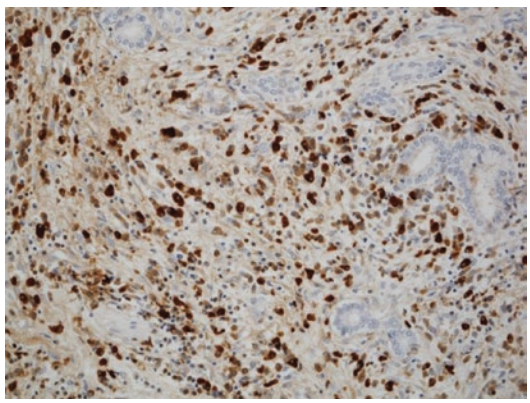

Fig. 4.5 IgG4 immunostaining in IgG4-related sclerosing cholangitis. Numerous positive cells are identified

Differential Diagnosis of IgG4-SC

Biliary Cancers

Distinction from biliary cancers is important but difficult for clinicians. In resected specimens, distinguishing the two diseases is not difficult for pathologists. However, cytological examination of bile juice or bile duct brushing can lead to misdiagnosis as cancer. It is also important to bear in mind that IgG4-SC has been reported to overlap in a few cases of biliary cancers [15, 16]. Such cases involve a minimally invasive cancer [15] or intraepithelial carcinoma/biliary intraepithelial neoplasia-3 [16], and thus careful evaluation of epithelial atypia is important when examining samples with IgG4-SC. IgG4-positive cells may be numerous in biliary cancers; IgG4-positive cells >50/HPF is reported in 9% of patients who had a resection for biliary cancer [12].

PSC

PSC is a progressive and devastating inflammatory condition of the bile duct that causes marked lymphoplasmacytic infiltration, fibrosis,

and subsequently biliary stenosis and wall thickening. PSC is common in patients with inflammatory bowel disease. So far, there is no effective treatment for PSC, and it is only curable by liver transplantation. In contrast to IgG4-SC, corticosteroids are ineffective. Stenosis in PSC is usually multifocal and involves large bile ducts through interlobular ducts. Stenotic lesions are often short compared to the long stricture of IgG4-SC, and small bile ducts are often obliterated with fibrosis. Histologically, PSC is characterized by an epithelium-centered inflammation and causes mucosal ulceration. When the ulceration is active, exudate on the surface and granulation tissue in the floor are observed (Fig. 4.6a). The granulation tissue is rich in neutrophils, histiocytes, lymphocytes, and plasma cells, and eosinophils may be numerous. Densely fibrous tissue surrounds the granulation tissue to reflect the repeated inflammation occurring at the site. In PSC, when the ulceration heals, epithelial regeneration and transmural fibrosis are found (Fig. 4.6b). The fibrosis seen in the bile duct wall is dense or even hyalinized and lacks inflammatory cells. IgG4-positive cells may be numerous even in PSC [13, 14]. Zen and colleagues [14] reported that IgG4-positive cells were >100/HPF in 2 out of 41 explanted PSC livers. However, numerous IgG4-positive cells are usually present in the actively inflamed foci of the large bile ducts, and they are absent in the peripheral portal tracts. Thus, it is uncommon to see numerous IgG4-positive cells in a liver biopsy from a PSC patient.

Biopsy Diagnosis of IgG4-SC

For the proper diagnosis of IgG4-SC, biopsy samples may be useful, but are not always helpful.

Bile Duct Biopsy

Samples obtained in bile duct biopsies are small and usually contain bile duct epithelium and only small amounts of connective tissue. Because lesions of IgG4-SC are present in the deep part of the bile duct wall, bile duct biopsies are not sufficient to make the diagnosis. However, bile duct biopsy is effective to exclude biliary cancers, and for this purpose, this examination is recommended. The presence of IgG4-positive cells >10/HPF is suggestive but not diagnostic of IgG4-SC, and for diagnosing IgG4-SC, characteristic histological features, such as storiform fibrosis and obliterative phlebitis, and appropriate clinical

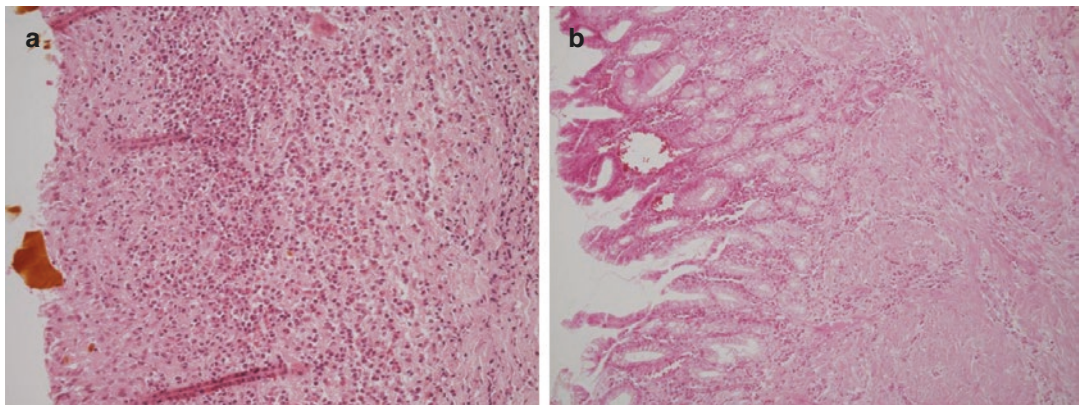

Fig. 4.6 Large duct lesions of primary sclerosing cholangitis. In an active state, the epithelial injury gives rise to ulcer formation (**a**). There is no epithelium (left), and histiocytes are aggregated on the surface, which is a reaction against the bile. Neutrophils, lymphocytes, and plasma cells are also present in the granulation tissue. When the ulceration heals, then dense fibrosis occurs in the bile duct wall (**b**). The epithelium (left) is regenerative in nature, and pyloric gland metaplasia is marked

settings are required. Cytological examination is also useful to exclude biliary cancers, but the diagnosis of IgG4-SC by IgG4 immunostaining on the cytological slides is not recommended, because IgG4-positive cells can be numerous in biliary cancers.

Liver Biopsy

Liver biopsy may be helpful but is usually not conclusive for diagnosing IgG4-SC. Supportive histological findings can be obtained in about 25% of liver biopsy samples and can be observed more frequently in cases with intrahepatic bile duct involvement [17]. The lesion called the portal-based fibroinflammatory nodule [18] is a tumefactive portal lesion consisting of fibroblasts, lymphocytes, and plasma cells. This finding is diagnostic of IgG4-SC, but it is very uncommon to find in a liver biopsy. The lesions in liver biopsies are usually peripheral portal tracts packed with lymphoplasmacytic infiltration with numerous (>10/HPF) IgG4-positive cells. Such lesions are found focally in liver biopsies. Inflammatory infiltration around the interlobular veins, in the lobules, and/or around the central veins may be also observed. Sclerosing cholangitis, storiform fibrosis, and obliterative phlebitis are usually absent, but they strongly support the diagnosis if present. Some histological findings of liver biopsies are helpful for distinguishing IgG4-SC from PSC; the vanishing of interlobular bile ducts and advanced stages of fibrosis (Ludwig's stages 3 and 4) are the features of PSC that are seldom observed in IgG4-SC, and IgG4-positive cells are more numerous in IgG4-SC than PSC [6, 19].

Histological Diagnostic Criteria

According to the clinical diagnostic criteria [20], IgG4-SC can be definitely diagnosed with at least three out of four of the following histological findings: (1) diffuse lymphoplasmacytic infiltration and fibrosis, (2) storiform fibrosis, (3) obliterative phlebitis, and (4) IgG4-positive cells >10/HPF. According to the consensus statement on the histological diagnosis of IgG4-RD, IgG4-positive cells need to be >50/HPF in the resected tissues and >10/HPF in biopsy materials in addition to an IgG4/IgG-positive cell ratio >40%. In addition, storiform fibrosis and/or obliterative phlebitis needs to be present to qualify histologically as highly suggestive of IgG4-SC. Histologically inconsistent cases, such as PSC, should not be considered IgG4-SC even if IgG4-positive cells are numerous.

Concluding Remarks

Because IgG4-SC has unique histological features, biopsy is expected to play a pivotal role in diagnosing it. However, it is difficult to obtain suitable biopsy samples in IgG4-SC cases because the lesions are located focally in sites where tissue acquisition is tough. Thus, pathological diagnosis is usually qualified with the word "possible" or "consistent." Even if the diagnosis is not conclusive, IgG4-SC also has characteristic clinical features, and discussion with clinicians and radiologists may solve the problem. It is also important to remember that some cases with biliary cancer have overlapping IgG4-SC, and the diagnosis of IgG4-SC does not necessarily exclude the diagnosis of biliary cancers.

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Clinical Features

5

Jong Kyun Lee

Introduction

The diagnosis of IgG4-SC requires a high index of suspicion and understanding of clinical features is the first step of suspicion. Early recognition of IgG4-SC may lead to proper management with corticosteroids and can eventually prevent organ failure that could possibly result from a delayed diagnosis. On the contrary, a misdiagnosis of IgG4-SC as other types of sclerosing cholangitis or cholangiocarcinoma may delay the optimal treatment or result in unnecessary operation. This chapter discusses various clinical features of IgG4-SC and compares with those of other disorders causing biliary strictures.

Demographics

IgG4-SC patients have a male preponderance and typically present in the sixth and seventh decades of life. In 2008, Ghazale et al. analyzed the large database of AIP patients at Mayo Clinic and described the clinical profiles and response to therapy of 53 patients with IgG4-SC [1]. The mean patient age was 62.2 years (range, 14–85 years) and 83% were older than age 50. The majority of patients were men (85%).

In 2015, Japanese nationwide survey was conducted regarding primary sclerosing cholangitis (PSC) and IgG4-SC, which enrolled all patients with IgG4-SC, irrespective of the presence or absence of AIP, with the largest case series of IgG4-SC patients reported to date [2]. This nationwide survey consisted of a questionnaire-based, multicenter, retrospective study. The male/female ratio was 436/91 (83%/17%), indicating male dominance in this disease. The median age was 66.2 years (range, 23.0–88.5 years), and the age distribution indicated that patients in their 60s had the highest risk for developing IgG4-SC (Fig. 5.1).

Clinical Presentation

The clinical presentation depends on the location, disease activity and the distribution of organs involved. Patients with IgG4-SC often present with obstructive jaundice (35–80%), pruritus, weight loss, abdominal pain, and cholangitis [1, 2] (Fig. 5.2). Abdominal pain usually does not require narcotics. It is extremely rare for patients with IgG4-SC to present with symptoms of decompensated cirrhosis [1]. However, no specific symptoms enable reliable differentiation of IgG4-SC from other causes of biliary obstruction. This fact is fundamentally important given

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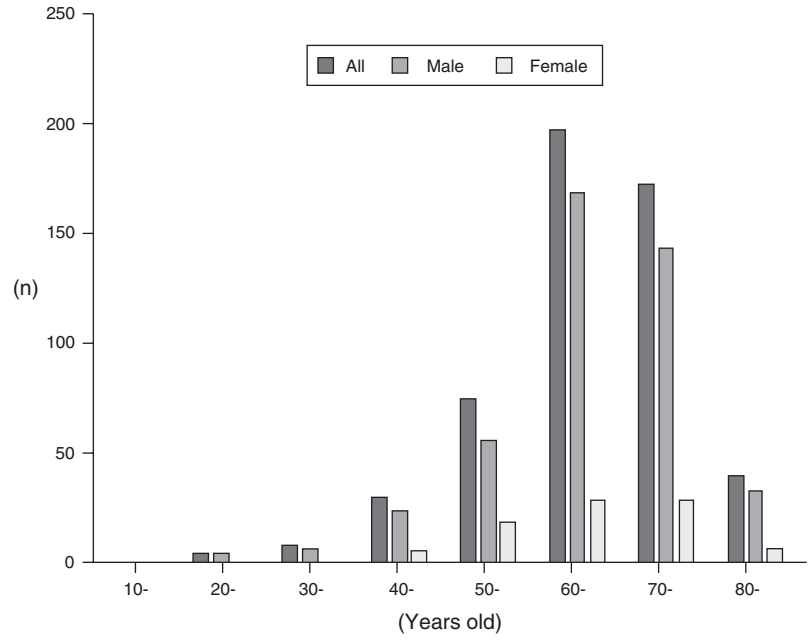

Fig. 5.1 Distribution of age at presentation, for patients with IgG4-related sclerosing cholangitis (Ref. [2])

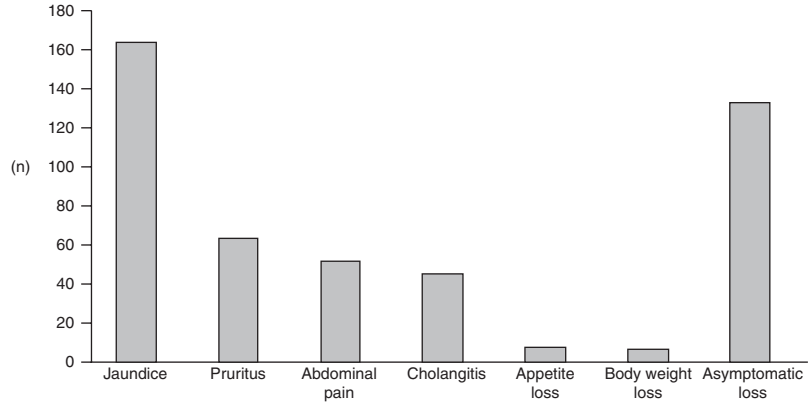

Fig. 5.2 Symptoms at presentation, for patients with IgG4-related sclerosing cholangitis (Ref. [2])

the serious consequences of misdiagnosis, which include surgical resection for presumed malignancy and inappropriate medical therapy [1, 3].

One-quarter of patients with IgG4-SC are asymptomatic or have nonspecific symptoms [2]. This finding suggests that, in the course of IgG4-SC, there is a latent phase without apparent symptoms before presentation. In such patients, IgG4-SC can be detected during the investigation of nonspecific symptoms or in the setting of abnormal liver function test results. IgG4-SC can also be found incidentally on cross-sectional imaging performed for other reasons.

IgG4-SC is included in the spectrum of IgG4-related disease, and some patients present with symptoms related to other organs affected by IgG4-RD. Other organ involvement is an important clue to the diagnosis of IgG4-SC. More than 90% of IgG4-SC patients have other organ involvements of IgG4-RD [1, 2]. The pancreas is most commonly involved. The presence of unexplained pancreatic disease in patients with biliary strictures should raise the suspicion for IgG4-SC. According to the literature, AIP was associated with 72–95% of the IgG4-SC patient population [1, 2, 4, 5]. Those with concomitant

AIP can present with symptomatic pancreatic exocrine and endocrine insufficiency such as steatorrhea and new-onset diabetes mellitus [1]. The different rate of association with AIP is most likely because of the different population of IgG4-SC whether isolated CBD stricture is included or not. Although pancreatic disease is present in the majority of IgG4-SC, patients who have no obvious pancreatic disease by clinical manifestations or image findings should not be excluded in the differential diagnosis. Attention should also be given to other organs that can be involved such as the salivary glands (sialoadenitis), retroperitoneum (retroperitoneal fibrosis), lymph nodes (mediastinal and axillary), or renal involvements.

In Japanese study, development of cholangiocarcinoma was reported in 0.8% [2]. In these patients, cholangiocarcinoma was diagnosed approximately at the same time as IgG4-SC (in two cases), or later (4 months and 4 years, respectively). Malignancies other than cholangiocarcinoma were detected in 21 patients, including lung cancer in 5, gastric cancer in 3, and duodenum cancer in 3. Overall, malignant diseases including cholangiocarcinoma were found in 25 patients with IgG4-SC (4.7%). However, the causal relationship between IgG4-SC and cholangiocarcinoma has not been documented.

Clinical Differences Between IgG4-SC and PSC

IgG4-SC should be differentiated from all disorders causing biliary strictures including PSC and cholangiocarcinoma because these conditions have entirely different therapeutic and prognostic implications. Classic PSC is generally refractory to steroid therapy, and liver transplantation is ultimately required due to liver failure, while cholangiocarcinoma generally requires surgical resection or chemotherapy. In contrast, IgG4-SC dramatically responds to steroid. Since various cholangiographic features of IgG4-SC are similar to those of PSC and cholangiocarcinoma, it is often difficult to discriminate IgG4-SC from these progressive or malignant diseases on the basis of cholangiographic findings alone. Therefore, multidisciplinary approach is very important in order to avoid the misdiagnosis of PSC and malignant diseases [1, 6, 7].

In particular, differential diagnosis between IgG4-SC and PSC can be confusing because of their similar manifestations, such as male predominance, cholestatic liver dysfunction of unknown etiology, and frequent stenosis of both the intrahepatic and extrahepatic bile ducts. Men appear to be more commonly affected by IgG4-SC same as PSC. However, no sex differences in incidence were noted in the PSC group in Japanese study [8]. Patient's age at clinical onset is around two decades older in IgG4-SC than in PSC. Very few cases have been reported in young adults less than 40 years of age (0–10%) [1, 4, 9]. In contrast, PSC tends to be a disease of young adults and middle-aged persons. The median age at diagnosis for PSC ranged from 35 to 41 years in Western countries [10, 11]. Interestingly, a Japanese nationwide survey for PSC demonstrated two unique peaks in age distribution (the first at 35–40 years and the second at 65–70 years) [12]. The age distribution of Korean patients with PSC corresponded to that of the Western population, rather than the Japanese population, as patients had a median age of 34 years and showed no second peak at older age. One plausible explanation for this discrepancy between Japan and Korea is that many older patients diagnosed with PSC in Japan might actually represent IgG4-SC patients, because the nationwide survey included various gastroenterologists with varying experience in PSC/IgG4-SC [4].

Obstructive jaundice is most frequently observed in patients with IgG4-SC, even when presenting isolated intrahepatic disease, reflecting marked concentric stenosis of the large bile duct. On the other hand, obstructive jaundice is rarely observed at diagnosis in PSC [4, 12].

And also, past history of AIP, concurrent pancreatic lesions, or extrabiliary involvement of other organs unusual for cholangiocarcinoma strongly suggests the possibility of IgG4-SC [1–4, 8, 12]. The majority of PSC patients have concomitant IBD, at a rate of 60–80% in Western countries [13, 14] and 30–50% in Japan [12, 15].

The coexistence of IBD in Korean patients with PSC corresponded to that of the Japanese population, as 41% of PSC patients have IBD [4]. In contrast, IBD is seldom associated with IgG4-SC patients (0–10%) [1, 8]. Backwash ileitis, rectal sparing, and low disease activity seem to be features that characterize IBD when it is associated with PSC [16]. If jaundice is prominent or progressive in patients with PSC, development of benign dominant strictures or cholangiocarcinoma should be considered.

Moon et al. compared patients with IgG4-SC (n = 39) and PSC (n = 76) who had intrahepatic/hilar strictures [4]. Most IgG4-SC patients (87%, 34 of 39) had a previous or concurrent IgG4-related disease; this was most frequently AIP (72%, 28 of 39). Among the five patients with isolated IgG4-SC, four (80%) needed surgical resection for the diagnosis of IgG4-SC. No patient had a history of IBD. PSC patients (41%, 41 of 76) had a history of IBD (30 patients, ulcerative colitis; 1 patient, Crohn's disease). Two patients had a history of diffuse pancreatic enlargement, which was eventually diagnosed as drug-induced acute pancreatitis. The clinical presentations of PSC were as follows: asymptomatic cholestatic liver dysfunction (47%), abdominal pain/discomfort (29%), jaundice (13%), and pruritus (7%).

Clinical Differences Between IgG4-SC and Cholangiocarcinoma

When stenosis develops in the hilar or intrahepatic bile duct, the cholangiographic appearance is similar to that of hilar cholangiocarcinoma. Because IgG4-SC responds well to steroids, but a diagnosis of hilar cholangiocarcinoma leads to hepatectomy, accurate differentiation between IgG4-SC and hilar cholangiocarcinoma is essential. There are few studies on differentiating IgG4-SC from hilar cholangiocarcinoma [17, 18]. IgG4-SC is particularly difficult to differentiate from hilar cholangiocarcinoma when it is not associated with AIP or when the diagnosis of AIP is unclear. Both diseases occurred predominantly in elderly males.

As the initial symptom, differential diagnosis between IgG4-SC and cholangiocarcinoma can be challenging as both diseases share several symptoms and signs [18]. Obstructive jaundice accompanied with skin pruritus, abdominal discomfort, and weight loss have been the most common symptoms in both IgG4-SC and cholangiocarcinoma patients. Obstructive jaundice occurred more frequently in patients with hilar cholangiocarcinoma. Obstructive jaundice may fluctuate during the course of IgG4-SC patients. The median serum total bilirubin levels were significantly higher in the patients with hilar cholangiocarcinoma. The serum CA19-9 levels are found to be significantly higher and more frequently elevate in hilar cholangiocarcinoma patients, but high level of the tumor marker CA 19-9 is also common in patients with IgG4-SC; therefore, CA19-9 levels do not seem to help to distinguish between IgG4-SC and cholangiocarcinoma [19].

Conclusion

Recognition of IgG4-SC requires familiarity with demographic and clinical features because they are the first step of suspicion. However, the diagnosis can be challenging in some patients because of the various presentations of the disease and similar presentations of other disorders causing biliary strictures. Therefore, IgG4-SC should be considered in the differential diagnosis in all patients with unexplained biliary strictures.

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Serum IgG4

6

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Introduction

Autoimmune pancreatitis (AIP) was reported in 2001 to be associated with high serum immunoglobulin (Ig)G4 levels [1]. Thereafter, elevated serum IgG4 was also detected in other diseases, such as dacryoadenitis/sialadenitis, retroperitoneal fibrosis, tubulointerstitial nephritis, lung disease, and sclerosing cholangitis (SC), which led to the proposal of a new disease concept called IgG4-related disease (IgG4-RD). Roughly 60–90% of patients with IgG4-related SC (IgG4-SC) have concomitant AIP and are relatively easy to identify. However, those with no increase in serum IgG4 and/or biliary lesions only can be difficult to diagnose. In particular, differentiation from hilar cholangiocarcinoma and primary SC (PSC) is challenging in IgG4-SC patients with biliary stenosis, which encompasses the hepatic portal and intrahepatic regions. While imaging and histopathological findings remain the most important means of diagnosing each disease, increased serum IgG4 levels have also become a useful diagnostic aid. In this chapter, we describe the roles and properties of serum IgG4, the relevance of serum IgG4 in various diseases, and finally outline the diagnostic value of serum IgG4 for IgG4-SC.

What Is the IgG4 Antibody?

IgG accounts for 70–75% of all human Igs and comprises four subclasses: G1, G2, G3, and G4. IgG4 normally represents only 3–6% of total IgG levels in the serum [2]. During immune responses, B cells that have reacted with antigens are activated and proliferate via antigen receptor-mediated signaling and CD40-mediated costimulation [3]. The B cells then differentiate into plasma cells to produce antibodies outside of follicles or remain inside follicles to form germinal centers differentiating into long-lived plasma cells or memory B cells. In activated B cells, the Ig heavy chain constant gene undergoes recombination for the production of IgG, IgE, and IgA while retaining antigenic specificity. This phenomenon is called class switching and occurs early in B cell activation. Cytokines such as interleukin (IL)-4, IL-10, and IL-21, which are produced by type 2 helper T (Th) cells, along with Th17 cells, regulatory T cells, and T follicular helper (Tfh) cells, may be involved in class switching to IgG4. Tfh cells are present in human peripheral blood and can be classified into Tfh1, Tfh2, and Tfh17 subsets. Tfh2 is closely related to IgG4 production and pathology in IgG4-RD [4].

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Roles of the IgG4 Antibody

Functions of IgG by Subclass

Different IgG subclasses have high homology in the primary structure of the heavy chain constant region but possess distinct structural, chemical, and biological properties (Table 6.1). In healthy adults, the serum levels of IgG subclasses are maintained at a relatively constant ratio. IgG3 is slightly larger in molecular weight than the other subclasses and has a half-life of approximately 1 week, which is shorter than 3 weeks for the IgG1, IgG2, and IgG4 subclasses. Several similarities exist between IgG1 and IgG3 and between IgG2 and IgG4 with respect to biological and immunological properties: IgG1 and IgG3 bind strongly to complements, while IgG2 exhibits weak, and IgG4 virtually no, complement binding. IgG4 secretion is notably induced against parasites and allergens.

Functions of IgG4

Fc–Fc Binding (Fig. 6.1)

The fragment crystallizable (Fc) region of IgG4 binds to the Fc region of other IgG subclasses to form IgG4–IgG complexes with an apparent structure in which Igs are polymerized around IgG4. IgG4 aggregated through this IgG4 FC–IgG Fc binding may elicit local inflammation in lesions via integrin. Alternatively, IgG4 can bind to IgG1-type immune complexes to form larger complexes, thereby facilitating immune complex clearance from affected local sites to end the pathological state. The Fc region of Igs also plays important roles in complement activation, and IgG4 binding to the Fc region of other IgG

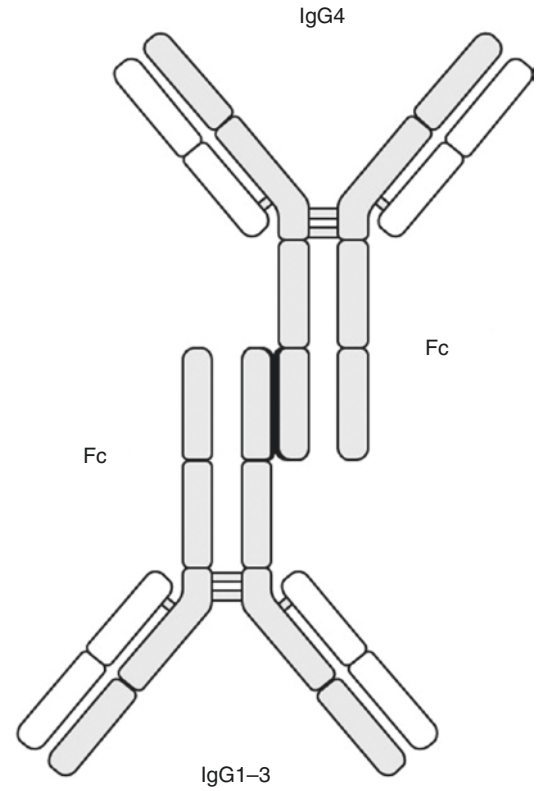

Fig. 6.1 Fc–Fc binding. IgG4 binds to other IgGs (IgG1–IgG3) via Fc–Fc interactions

Table 6.1 Characteristics of IgG subclasses (Adapted from Ochs et al. [2] with modifications)

	IgG1	IgG2	IgG3	IgG4
Heavy chain	γ1	γ2	γ3	γ4
Molecular weight ($\times 10^3$)	146	146	165	146
Molecular weight of the heavy chain ($\times 10^3$)	51	51	60	51
Average serum level in adults (mg/dl)	840	240	80	40
Percentage of total serum IgG (%)	60–70	20–25	5–10	3–6
Biological half-life (day)	20–25	20–23	7–9	20–25
Complement activation				
Classical pathway	++	+	++	–
Alternative pathway	–	–	–	±
Allergen				
Mites	+	–	–	++
Pollen	+	–	–	++

subclasses can block the Fc-mediated inflammation process [5].

Fab Arm Exchange (Fig. 6.2)
IgG4 is typically secreted in the form of a dimer of weakly binding subunits. Unlike other IgG subclasses, the fragment antigen-binding (Fab) arms of IgG4 are exchanged with those of other IgG4 molecules, and the resulting antibody can recognize two different antigens. This so-called Fab arm exchange creates bispecific IgG4 that does not cross-link antigens and exhibits anti-inflammatory effects by decreasing the formation of immune complexes [6].

Diseases with Possible Pathological Involvement of IgG4

With its unique features of Fc–Fc binding, Fab arm exchange, and very low complement binding ability, IgG4 generally acts in immune response suppression. However, IgG4 also reportedly plays a pathogenic role in several diseases, as listed in Table 6.2 and described as follows:

Pemphigus Vulgaris and Pemphigus Foliaceus

Pemphigus vulgaris and pemphigus foliaceus are autoimmune skin diseases caused by antibodies against desmoglein 3 and 1. The anti-desmoglein autoantibodies are predominantly of the IgG4 subclass and are considered to be pathogenic after disease reproduction in mice receiving autoantibodies [7].

Table 6.2 Diseases with reported pathological involvement of IgG4

Pemphigus vulgaris and pemphigus foliaceus
Rheumatoid arthritis
Thrombotic thrombocytopenic purpura
Anti-MuSK antibody-positive myasthenia gravis
Allergic disease
IgG4-related disease

Rheumatoid Arthritis

IgG4 rheumatoid factors (RFs) are present in the serum and synovial fluid of patients with rheumatism. Although conventional RF binds via variable regions, IgG4 RF is reportedly mediated by nonspecific Fc–Fc binding. Elevated IgG4 levels in joints may be responsible for persistent, chronic synovial inflammation in patients with rheumatoid arthritis [8].

Thrombotic Thrombocytopenic Purpura

IgG subclass analysis of anti-ADAMTS13 antibodies has revealed the highest frequencies (90%) for IgG4 class autoantibodies, which may therefore play a central role in the immune response to this disease. Thrombotic thrombocytopenic purpura recurrence is more likely to occur in patients with high IgG4 and low IgG1 levels [9].

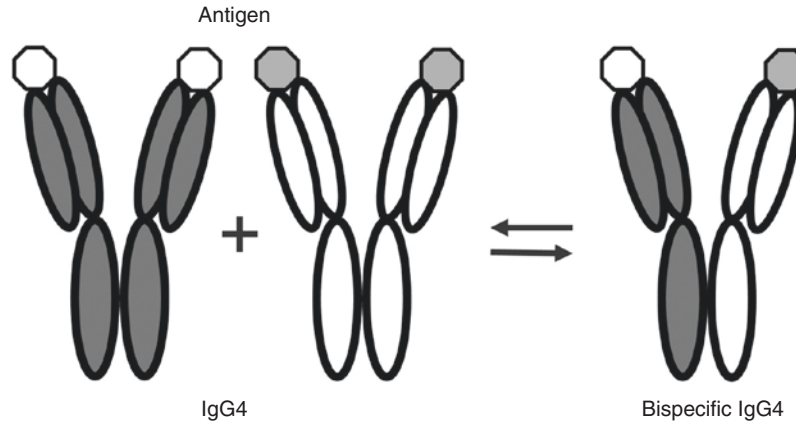

Fig. 6.2 Fab arm exchange. The characteristics of bispecific IgG4 are as follows: loss of monospecific cross-linking activity, inability to form immune complexes, and anti-inflammatory effects

Anti-Muscle-Specific Kinase (MuSK) Antibody-Positive Myasthenia Gravis

IgG4 antibodies against the MuSK found in neuromuscular junctions are believed to be critical in disease pathology. Patient anti-MuSK antibodies are predominantly IgG4, and injected IgG from anti-MuSK-positive patients can reproduce the pathology of myasthenia gravis in mice [10].

Allergic Diseases

In allergic diseases, IgG4 is produced along with antigen-specific IgE because the IL-4 derived from allergen-specific T cells acts as a class-switching factor for IgE and IgG4. After regulatory T cells are induced, antigen-specific IgG4 titer becomes increased by hyposensitization therapy [11]. However, there remains debate on whether IgG4 enhances or suppresses allergic reactions.

IgG4-RD

Although IgG4-RD is considered by most to be an autoimmune disease, the precise role of IgG4 in IgG4-RD remains elusive. Shiokawa et al. [12] demonstrated the pathogenicity of IgG4 by showing that lesions were induced in the pancreas and salivary glands in mice injected with IgG, IgG1, and IgG4 from patients with IgG4-RD. They also witnessed that when IgG1 was coadministered with IgG4, it tended to show a reduced pathogenicity level than when injected alone. This result uncovered two sides of IgG4 in IgG4-RD; although IgG4 has weak pathogenicity, it can nonetheless suppress the pathogenicity of IgG1.

Serum IgG4 in IgG4-SC

Diagnostic Value of IgG4 in IgG4-SC

The disease concept of IgG4-RD includes elevated serum IgG4 levels as a hallmark diagnostic criterion. However, apart from AIP, there have been insufficient studies to establish precise cutoff values for IgG4-RD. Based on the clinical diagnostic criteria of IgG4-SC published in 2012 [13], hyper-IgG4-emia, defined as IgG4 levels of ≥135 mg/dl using nephelometry, has been accepted as a diagnostic item. In IgG4-SC, high serum IgG4 levels (i.e., ≥135 mg/dl) were present in 90% of patients [14, 15], but the reported sensitivity (64–90%) and specificity (87–93%) of hyper-IgG4-emia for diagnosing IgG4-SC have varied widely, presumably due to differences in assay methods and measurement kits, frequency of complicating type 1 AIP, and control group variance worldwide. Thus, although hyper-IgG4-emia is frequent in IgG4-SC and useful in diagnosis, it is not sufficiently specific such that cholangiocarcinoma (CC) and PSC can be ruled out solely on the basis of serological findings.

Differentiation from Cholangiocarcinoma

High serum IgG4 levels are absent in 10% of IgG4-SC patients and exist in 8–14% of patients with CC [14, 16]. Hence, there is a high risk of misdiagnosis when differentiating between IgG4-SC and CC using hyper-IgG4-emia alone as a benchmark. Conventional cutoff values have been determined on the basis of investigations of CC and multiple other diseases, including pancreatic cancer, PSC, and primary biliary cirrhosis. Serum IgG4 levels differ slightly from one disease to another, and IgG4 elevation (≥135 mg/dl) can be found at certain frequencies among each. Accordingly, a broad serum IgG4 cutoff value of >135 mg/dl may be useful for distinguishing IgG4-SC from CC. To achieve more accurate differentiation, the cutoff value needs to be set to at least twice the upper limit of the normal range, while a value of four times the upper limit of normal range yields a specificity of 99–100% [14, 16]. Meanwhile, IgG4-SC has been classified into four types based on cholangiographic findings [17] that are differentiated depending on the site of the lesion: type 1 IgG4-SC should be distinguished from chronic pancreatitis, distal CC, and pancreatic cancer when stenosis is present in the lower biliary duct,

type 2 IgG4-SC from PSC when a broad internal region is affected, and type 3 and 4 IgG4-SC from hilar CC when stenosis is present in the hepatic portal region. An IgG4 cutoff value of 207 mg/dl is reportedly useful for the differential diagnosis of type 3 and 4 IgG4-SC with lesions in the hepatic portal region, where CC is an important disease to rule out [14]. However, differentiating IgG4-SC from CC based only on serum IgG4 levels remains difficult, and thus comprehensive diagnosis with consideration of imaging and histopathological findings is ultimately necessary.

Table 6.3 Performance of serum IgG4 in distinguishing IgG4-SC from CC and PSC

	IgG4 cutoff value (mg/dl)	Sensitivity (%)	Specificity (%)	Citation
IgG4-SC vs. CC	138	89.8	92.6	14
	140	78	87	16
	280	50	97	
	560	26	100	
IgG4-SC vs. PSC	117	91.5	87.6	14
	140	90	85	15
	250	89	95	
	250	67[a]	95[a]	
	280	70	98	
	560	42	100	

[a]Validation cohort

Differentiation from PSC

High serum IgG4 levels are also found in 9–26% of PSC patients [14, 15, 18, 19]. The reported sensitivity and specificity of differentiating IgG4-SC from PSC at an IgG4 cutoff value of 117 mg/dl were 91.5% and 87.6%, respectively [14], which changed when different cutoffs were adopted (e.g., 90% and 85%, respectively, with 140 mg/dl; 70% and 98%, respectively, with 280 mg/dl; and 42% and 100%, respectively, with 560 mg/dl) [15]. As some studies have demonstrated that a serum IgG4 cutoff value of four times the upper limit of normal range can be useful for accurate differentiation, IgG4 appears to be of greatest utility for cases of severely increased serum levels. However, it may not have sufficient reliability for diagnosing patients with moderately increased serum IgG4; a cutoff value of 250 mg/dl afforded a sensitivity and specificity of 89% and 95%, but sensitivity fell to 67% in a different cohort. The sensitivity and specificity of diagnosing various diseases using serum IgG4 levels are summarized in Table 6.3. The use of the IgG4:IgG1 ratio has also been recommended for patients with IgG4 levels of less than twice the upper limit of normal, with a sensitivity and specificity of 86% and 95%, respectively, using an IgG4:IgG1 ratio cutoff value of 0.24 in patients with clinically elevated serum IgG4 [15]. IgG4-SC and PSC exhibit similar bile duct images but differ substantially in their treatment and prognosis. While corticosteroids elicit a good response in IgG4-SC, liver transplantation is the only therapeutic treatment option for advanced PSC. Accurate differential diagnosis is also important for determining appropriate care plans, for which data obtained on the basis of serum IgG4 levels are valuable. However, there are clear limitations to diagnoses based on serum IgG4 levels alone, and thus additional data, such as the presence or absence of lesions suggestive of IgG4-RD in other organs, histopathological findings from liver or bile duct biopsy, and biliary duct and other imaging findings, are crucial.

IgG4 Levels in Bile

Several recent pilot studies have reported that IgG4 levels in the bile are significantly elevated in patients with IgG4-SC and can be useful for distinguishing IgG4-SC from lower biliary strictures owing to other causes, such as SC, cholangiocarcinoma, and pancreatic cancer [19, 20]. This method of measuring IgG4 in the bile appears to be more effective for differential diagnosis in patients with low-to-moderately increased serum IgG4 than in those with abnormally high values. Moreover, bile can be safely collected without any special procedures in patients undergoing endoscopic retrograde cholangiopancreatography and IgG4 levels assessed inexpensively using conventional methods. Once

the efficacy of this method is validated in larger cohorts, bile-based measurement of IgG4 is expected to contribute greatly to the timely and accurate diagnosis of IgG4-SC.

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Diagnostic Criteria

7

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Diagnostic Criteria of IgG4-Related Sclerosing Cholangitis

Introduction

IgG4-related sclerosing cholangitis (IgG4-SC) is a characteristic type of sclerosing cholangitis with an unknown pathogenic mechanism. IgG4-SC patients have increased serum IgG4 levels [1] and dense infiltration of IgG4-positive plasma cells with extensive fibrosis in the bile duct wall [2]. IgG4-SC is frequently associated with autoimmune pancreatitis (AIP) and generally shows a good prognosis and responds to steroid therapy [3–7].

As various cholangiographic features of IgG4-SC are similar to those of primary sclerosing cholangitis (PSC), pancreatic cancer, and cholangiocarcinoma [8, 9], it can be difficult to discriminate IgG4-SC from these progressive or malignant diseases on the basis of cholangiographic findings alone [10, 11]. Therefore, these three diseases should be taken into account in the diagnostic criteria for IgG4-SC.

Diagnostic Criteria

Two sets of diagnostic criteria for IgG4-SC have been proposed. The HISORt criteria were originally developed for AIP and adapted for IgG4-SC [7] (Table 7.1). These criteria are based on histological findings, imaging, serological examination, other organ involvement, and response to steroid therapy.

A second set of diagnostic criteria for IgG4-SC has been proposed by a Japanese group [12] (Table 7.2). Diagnosis of IgG4-SC is based on the following four criteria: (1) characteristic biliary imaging findings, (2) elevation of serum IgG4 concentration, (3) coexistence of IgG4-related diseases except those of the biliary tract, and (4) characteristic histopathological features. The effectiveness of steroid therapy is an optional extra diagnostic criterion used to confirm a diagnosis of IgG4-SC. Furthermore, the typical cholangiographic features are shown schematically and diseases to be discriminated from IgG4-SC and the necessary examinations for diagnosis are described to facilitate clinical application of these diagnostic criteria [12] (Fig. 7.1).

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Table 7.1 Diagnostic criteria with histologic and imaging findings, serum tests, organ manifestation pattern, and response to immunosuppressive therapy (HISORt criteria) for IgG4-related sclerosing cholangitis (cited from [7])

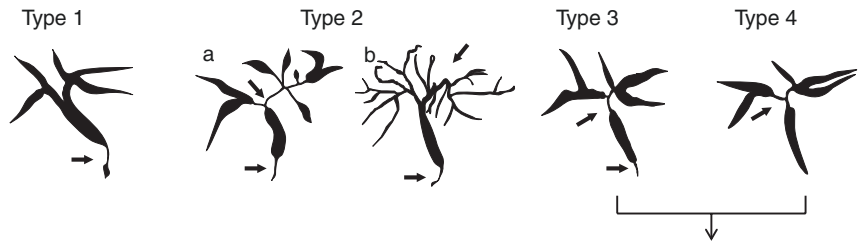
Feature	Characteristics
Histology of bile duct	Lymphoplasmacytic sclerosing cholangitis on resection specimens (lymphoplasmacytic infiltrate with >10 IgG4-positive cells/HPF within and around bile ducts with associated obliterative phlebitis and storiform fibrosis)[a]
Imaging of bile duct	One or more strictures involving intrahepatic, proximal extrahepatic, or intrapancreatic bile ducts fleeting/migrating biliary strictures
Serology	Increased levels of serum IgG4
Other organ involvement[b,c]	Pancreas, classic features of autoimmune pancreatitis on imaging or histology[d]; suggestive pancreatic imaging findings, focal pancreatic mass/enlargement without pancreatic duct dilatation, multiple pancreatic masses, focal pancreatic duct stricture without upstream dilatation, pancreatic atrophy Retroperitoneal fibrosis Renal lesions: single or multiple parenchymal low-attenuation lesions (round, wedge-shaped, or diffuse patchy) Salivary/lacrimal gland enlargement
Response to steroid therapy	Normalization of liver enzyme levels or resolution of stricture[e]

[a]Bile duct biopsy specimens often do not provide sufficient tissue for a definitive diagnosis. In such specimens, IgG4 immunostaining showing >10 IgG4-positive cells/HPF is suggestive of IgG4-related sclerosing cholangitis (IgG4-SC); however, the specificity of this finding is not known
[b]IgG4 immunostaining of involved organs shows >10 IgG4-positive cells/HPF
[c]The presence of inflammatory bowel disease (IBD) suggests primary sclerosing cholangitis rather than IgG4-SC; however, the absence of IBD does not help diagnose IgG4-SC in an individual patient
[d]Diffusely enlarged pancreas with delayed enhancement and capsule-like rim. Diffusely irregular, attenuated main pancreatic duct multiple strictures or long stricture without upstream dilatation
[e]Complete resolution of stricture may not be seen in all patients, especially those early in the course of treatment (<6 weeks) or with predominantly fibrotic strictures

Table 7.2 Clinical diagnostic criteria of IgG4-related sclerosing cholangitis 2012 (cited from [12])

A. Diagnostic criteria
1. Biliary tract imaging reveals diffuse or segmental narrowing of the intrahepatic and/or extrahepatic bile duct associated with the thickening of bile duct wall
2. Hematological examination shows elevated serum IgG4 concentrations (≥135 mg/dl)
3. Coexistence of autoimmune pancreatitis, IgG4-related dacryoadenitis/sialadenitis, or IgG4-related retroperitoneal fibrosis
4. Histopathological examination shows: (1) Marked lymphocytic and plasmacyte infiltration and fibrosis (2) Infiltration of IgG4-positive plasma cells, >10 IgG4-positive plasma cells/HPF (3) Storiform fibrosis (4) Obliterative phlebitis
Option: effectiveness of steroid therapy A specialized facility, in which detailed examinations such as endoscopic biliary biopsy and endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) can be administrated, may include in its diagnosis the effectiveness of steroid therapy, once pancreatic or biliary cancers have been ruled out.
B. Diagnosis
Definite diagnosis: 1 + 3, 1 + 2 + 4 (1) (2), 4 (1) (2) (3), 4 (1) (2) (4) Probable diagnosis: 1 + 2 + option Possible diagnosis: 1 + 2

Note: It is necessary to exclude primary sclerosing cholangitis, malignant diseases such as pancreatic or biliary cancers, and secondary sclerosing cholangitis caused by the diseases with obvious pathogenesis. If IgG4-related sclerosing cholangitis cannot be clinically ruled out, a patient must not be treated with facile steroid therapy but should be referred to a specialized medical facility



Differential diagnosis	Pancreatic cancer Bile duct cancer Chronic pancreatitis	Primary sclerosing cholangitis	Bile duct cancer Gallbladder cancer
Useful modalities	IDUS* (bile duct) EUS-FNA** (pancreas) Biopsy (bile duct)	Liver biopsy Colonoscopy (R/O coexistence of IBD ***)	EUS (bile duct, pancreas) IDUS (bile duct) Biopsy (bile duct)

Fig. 7.1 The cholangiographic classification of IgG4-related sclerosing cholangitis and differential diagnosis. Stenosis is located only in the lower part of the common bile duct in Type 1; stenosis is diffusely distributed in the intra- and extrahepatic bile ducts in Type 2. Type 2 is further subdivided into two types. Extended narrowing of the intrahepatic bile ducts with prestenotic dilation is widely distributed in Type 2a. Narrowing of the intrahepatic bile ducts without prestenotic dilation and reduced bile duct branches is widely distributed in Type 2b; stenosis is detected in both the hilar hepatic lesions and the lower part of the common bile ducts in Type 3; and strictures of the bile duct are detected only in the hilar hepatic lesions in Type 4. * IDUS: intraductal ultrasonography. ** EUS-FNA: endoscopic ultrasound-guided fine-needle aspiration. *** IBD: inflammatory bowel disease

Diagnostic Imaging Findings

Narrowing of the Bile Duct

IgG4-SC shows various cholangiographic features similar to those of pancreatic cancer, PSC, and cholangiocarcinoma. The characteristic features of IgG4-SC can be classified into four types based on the stricture regions revealed by cholangiography and differential diagnosis (Fig. 7.1) [13].

Type 1 IgG4-SC shows stenosis only in the lower part of the common bile duct, which should be differentiated from chronic pancreatitis, pancreatic cancer, and cholangiocarcinoma. IgG4-SC associated with AIP frequently shows a stricture in the lower common bile duct. This stricture can originate from thickening of the bile duct or the effect of pancreatic inflammation and/or edema [14].

Type 2 IgG4-SC, in which stenosis is diffusely distributed throughout the intrahepatic and extrahepatic bile ducts, should be differentiated from PSC. Band-like stricture, a beaded and pruned tree appearance, and diverticulum-like outpouching are significantly more frequent in PSC. In contrast, segmental strictures, long strictures with prestenotic dilation, and strictures of the lower common bile duct are significantly more common in IgG4-SC. Type 2 is subdivided into Type 2a, which involves narrowing of the intrahepatic bile ducts with prestenotic dilation, and Type 2b, which involves narrowing of the intrahepatic bile ducts without prestenotic dilation and reduced bile duct branches. The latter is caused by marked lymphocytic and plasmacyte infiltration into the peripheral bile ducts.

Type 3 IgG4-SC is characterized by stenosis in both the hilar hepatic lesions and the lower part of the common bile duct. Type 4 IgG4-SC shows strictures of the bile duct only in hilar hepatic lesions. The cholangiographic findings of Types 3 and 4 should be discriminated from those of cholangiocarcinoma.

Thickening of the Bile Duct

Abdominal ultrasonography (US) [15], abdominal computed tomography [16], abdominal magnetic resonance imaging, endoscopic ultrasonography, and intraductal ultrasonography (IDUS) [17] show circular-symmetric wall thickening, smooth outer and inner margins, and homogenous internal echo. These characteristic features are recognized not only in the stenotic areas or occasionally in the gallbladder but also in areas without stenosis that appear normal on

cholangiogram. Bile duct wall thickening extends continuously from the intrapancreatic bile duct to the upper bile duct in most IgG4-SC cases. To differentiate IgG4-SC from cholangiocarcinoma, a bile duct wall thickness of 0.8 mm that appears normal on a cholangiogram is the optimum cutoff established by a study on IDUS [17]. Patients with PSC also have widespread thickening of the bile duct, which shows IDUS findings of an irregular inner margin, diverticulum-like outpouching, and disappearance of three layers [18].

Hematological Examination

An elevated serum IgG4 level is a diagnostic criterion for IgG4-SC [1]. The cutoff serum IgG4 levels are 140 mg/dl (nephelometric method) in the HISORt criteria [7] and 135 mg/dl in the Japanese criteria [12].

However, an elevated serum IgG4 level is also observed in atopic dermatitis, pemphigus, asthma, etc.; in particular, elevated serum IgG4 levels are also observed in PSC and some malignant cholangiopancreatic diseases (e.g., pancreatic cancer and cholangiocarcinoma) [19, 20]. Oseini et al. evaluated the utility of serum IgG4 level to discriminate IgG4-SC from cholangiocarcinoma [20]. They concluded that some patients with cholangiocarcinoma, particularly PSC, had elevated serum IgG4 levels, and diagnosis using a twofold higher cutoff serum IgG4 level (>280 mg/dl) may not reliably distinguish IgG4-SC from cholangiocarcinoma. A cutoff level fourfold higher than the upper limit of normal (> 560 mg/dl) had 100% specificity for IgG4-SC.

A Japanese multicenter study was performed to establish a serum IgG4 cutoff value to differentiate IgG4-SC from pancreatic cancer, PSC, and cholangiocarcinoma [21]. A total of 344 IgG4-SC patients were enrolled, together with 245, 110, and 149 patients with pancreatic cancer, PSC, and cholangiocarcinoma, respectively, as controls. The cutoff values from receiver operating characteristic (ROC) curves showed similar sensitivity and specificity to that of 135 mg/dl when all IgG4-SC cases and controls were compared. Of the pancreatic cancer, PSC, and cholangiocarcinoma cases, 5.7%, 12.7%, and 8.1%, respectively, had serum IgG4 levels higher than the cutoff value. A serum IgG4 cutoff value of 182 mg/dl increased the specificity to 96.6% for distinguishing Types 3 and 4 IgG4-SC from cholangiocarcinoma, and a cutoff of 207 mg/dl enabled discrimination of Types 3 and 4 IgG4-SC from cholangiocarcinoma.

Other Organ Involvement

IgG4-SC is frequently associated with AIP. Ghazale et al. reported that 49 of 53 patients with IgG4-SC had AIP [7]. In a Japanese multicenter study, 329 of 344 (95.6%) IgG4-SC cases were associated with AIP [21]. Association with AIP is useful for diagnosis of IgG4-SC. However, some IgG4-SC patients do not have AIP and are thus difficult to diagnose; most isolated IgG4-SC cases have hilar biliary strictures [22–24].

Occasionally, IgG4-SC is associated with other systemic IgG4-related diseases, including IgG4-related symmetrical dacryoadenitis/sialadenitis, IgG4-related retroperitoneal fibrosis, and IgG4-related kidney disease [25–28]. These associations can also assist diagnosis of IgG4-SC. Inflammatory bowel disease is usually not an associated condition, unlike its frequent association with PSC [29].

Pathological Findings of the Bile Duct

In IgG4-SC cases, fibroinflammatory involvement is observed mainly in the submucosa of the bile duct wall, whereas the bile duct epithelium is intact [30]. However, slight injury and/or neutrophil infiltration are occasionally observed in cases of IgG4-SC with secondary cholangitis. PSC should be excluded if inflammation is observed, particularly in the bile duct wall epithelium.

Endoscopic transpapillary bile duct biopsy is performed to rule out cholangiocarcinoma. Ghazale et al. reported that the immunostaining results of 14 (88%) of 16 patients indicated abundant IgG4+ cells in bile duct biopsy specimens [7]. However, it is difficult to obtain

enough biliary tract tissue to assess the histology of IgG4-SC biopsy specimens (e.g., storiform fibrosis and obliterative phlebitis) [13]. We were able to diagnose IgG4-SC in only 3 (18%) of 17 patients on the basis of its characteristic histopathological features [17]. In addition, 1 of 11 cholangiocarcinoma cases presented abundant IgG4+ plasma cells. Zhang et al. also reported abundant IgG4+ plasma cells in 7 (18%) of 38 cases of cholangiocarcinoma [31]. It is important to note that the superficial nature of endoscopic biopsy specimens limits their usefulness for demonstrating the characteristic histological features of IgG4-SC.

Ampullary biopsy is occasionally useful in the diagnosis of IgG4-SC patients with swelling of the pancreatic head caused by AIP [32]. Liver biopsy can be useful for diagnosing IgG4-SC cases with intrahepatic bile duct strictures [33, 34].

Exclusion of Secondary Sclerosing Cholangitis

It is necessary to rule out the following features of secondary sclerosing cholangitis: common bile duct stone, cholangiocarcinoma, trauma, biliary tract surgery, congenital biliary anatomy, corrosive cholangitis, ischemic bile duct stenosis, AIDS-related cholangitis, and biliary injury due to intra-arterial chemotherapy.

Effectiveness of Steroid Therapy

In the HISORt criteria, response to steroid treatment is defined as a decrease in liver enzyme levels to less than twofold the upper limit of normal and/or improvement in biliary strictures [7]. In the Japanese criteria, this optional diagnostic criterion should be applied only to IgG4-SC cases in which the effect of steroid therapy can be evaluated by imaging modalities after negative work-up for malignancy [12]. Accordingly, clinical conditions or hematological findings cannot be evaluated by this method. It is sometimes difficult to obtain sufficient biopsy specimens from patients suffering from diseases not only of the biliary tract but also of other organs, such as the pancreas, lachrymal gland, salivary gland, and retroperitoneum. However, efforts should be made to collect sufficient tissue samples for diagnosis, and steroid trials should be avoided [12].

The effectiveness of steroid therapy should be cautiously evaluated because some malignant lesions improve after steroid administration [35]. If neoplastic lesions cannot be clinically ruled out after steroid therapy, a reevaluation should be performed to rule out malignant cholangiopancreatic diseases.

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Imaging: US and CT

8

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IgG4-related disease (IgG4-RD) is characterized by increased serum levels of IgG4, a lymphoplasmacytic infiltrate composed of IgG4-positive plasma cells, storiform fibrosis, obliterative phlebitis, and mild to moderate eosinophilia [1]. IgG4-related sclerosing cholangitis (IgG4-SC) is a biliary lesion associated with IgG4-RD, which is frequently seen in elderly men, characterized by obstructive jaundice owing to a bile duct stricture and responds well to steroid therapy [2]. Recently, the first clinical diagnostic criteria for IgG4-SC were proposed in Japan [3]. As in the diagnostic items of the 2012 IgG4-SC diagnostic criteria, biliary tract imaging of IgG4-SC reveals diffuse or segmental narrowing of the intrahepatic and/or extrahepatic bile duct associated with thickening of the bile duct wall [3].

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The correct diagnosis for IgG4-SC prior to steroid therapy should be essential and toward this, understanding the characteristic imaging features for IgG4-SC; however, the diffuse cholangiographic abnormalities observed in IgG4-SC may resemble those observed in other disease such as primary sclerosing cholangitis (PSC), and the presence of segmental stenosis suggests cholangiocarcinoma (CC) [2, 4]. In this chapter, ultrasonography (US) and computed tomography (CT) findings of IgG4-SC are reviewed, and the points for differentiating other disease are discussed.

US Findings

Abdominal ultrasonography (US) is noninvasive imaging modality. It is usually performed for the initial imaging examination following blood tests in patients with symptoms such as jaundice, liver dysfunction, exacerbation of diabetes mellitus, or abdominal pain. It can be also performed for the medical check with no symptom [5].

In a case with IgG4-SC, US detects thickening of the wall of the common bile duct characterized by layered or parenchymal hypoechoic wall thickening [5, 6]. In some cases, thickening of duct wall beyond extrahepatic bile ducts extends to intrahepatic bile ducts [5]. The detection of the narrowing of the intrapancreatic bile duct and stricture of hilar or intrahepatic bile ducts by US may be hard [5],

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and other imaging modalities should be required. When diffuse type autoimmune pancreatitis (AIP) is complicated, US displays a diffusely enlarged pancreas as a hypoechoic area presenting a "sausage-like" appearance [7] (Fig. 8.1a). The enlarged hypoechoic area contains scattered hyperechoic spots. In patients with a segmentally or focally enlarged pancreas, AIP is important to differentiate from pancreatic ductal adenocarcinoma or mass-forming pancreatitis [8]. In some patients with AIP, US detects thickening of the gallbladder wall [9] (Fig. 8.1b). US also detected thickening of the wall of the common bile duct in such patient. Kamisawa et al. reported that gallbladder wall thickening was more frequent in AIP patients with extensive bile duct involvement ($p < 0.01$) [10].

CT Findings

The patients with IgG4-SC usually exhibit the CT findings including narrowing of long segments of the biliary system and contrast enhancement of the biliary wall in regions affected by strictures [2]; however misdiagnosis with cholangiocarcinoma could occur. Figure 8.1 shows the typical contrast-enhanced CT imaging of the IgG4-SC: concentric circle-formed wall thickening of the bile duct in the early phase as well as delayed phase (Fig. 8.2a, b) with smooth inner and outer margin. The wall thickening of the bile duct spreads widely from lower to upper common bile duct (CBD) (Fig. 8.2c, d). The features of bile duct wall thickening and bile duct stricture can be improved after steroid therapy (Fig. 8.3). Some atypical case of IgG4-SC showed no biliary stricture but severe thickening of the bile duct wall [11] (Fig. 8.4).

Yata et al. compared and analyzed the MDCT findings of the patients with IgG4-SC ($n = 33$) and extrahepatic cholangiocarcinoma (EH-CC $n = 39$), retrospectively [2]. In that study, the following CT findings were evaluated:

(a) Location (involving intrapancreatic bile duct, not involving intrapancreatic bile duct)
(b) The presence or absence of biliary wall thickening and masses (wall thickening alone, a mass alone, or wall thickening t mass)
(c) Wall concentricity (concentric, eccentric)
(d) Outer margin status (smooth, irregular)
(e) Visibility of the lumen (fully visible, not fully visible, or invisible)
(f) Inner margin status (smooth, irregular)
(g) Funnel-shaped proximal bile duct (present, absent)
(h) Funnel-shaped distal bile duct (present, absent)
(i) Skip lesions (present, absent)
(j) Abnormal pancreatic findings: (1) enlargement of the pancreas, (2) a capsule-like rim, (3) unenhanced regions of the pancreas, and (4) enhancement of the main pancreatic duct (present, absent) [2]

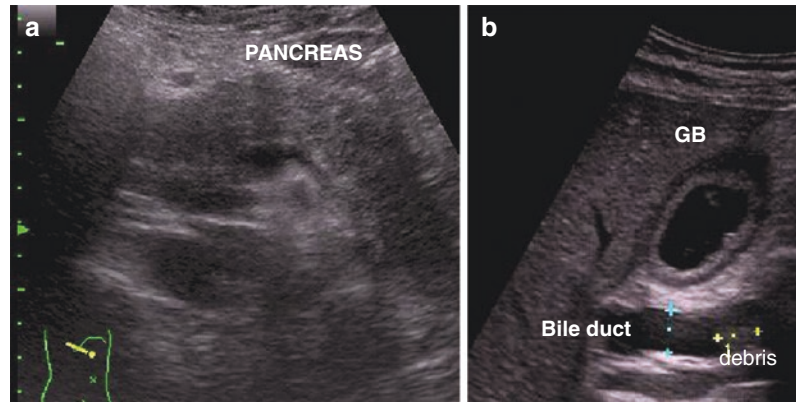

Fig. 8.1 A case of AIP. US display diffusely enlarged pancreas, as "sausage-like" appearance" (**a**). US also show CBD dilatation and thickening of the gallbladder wall with a homogeneous internal echo in the third layer structure (**b**)

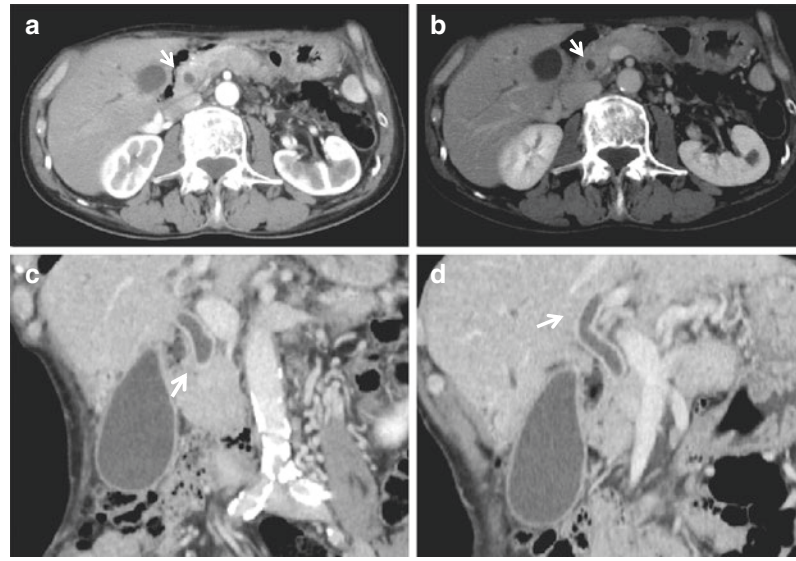

Fig. 8.2 A case with IgG4-SC. Enhanced CT shows the concentric circle-formed wall thickening of the bile duct: (**a**) early phase and (**b**) delayed phase. The outer and inner margin of the bile duct is smooth. The wall thickening of the bile duct spreads widely from lower to upper common bile duct (**c** and **d**)

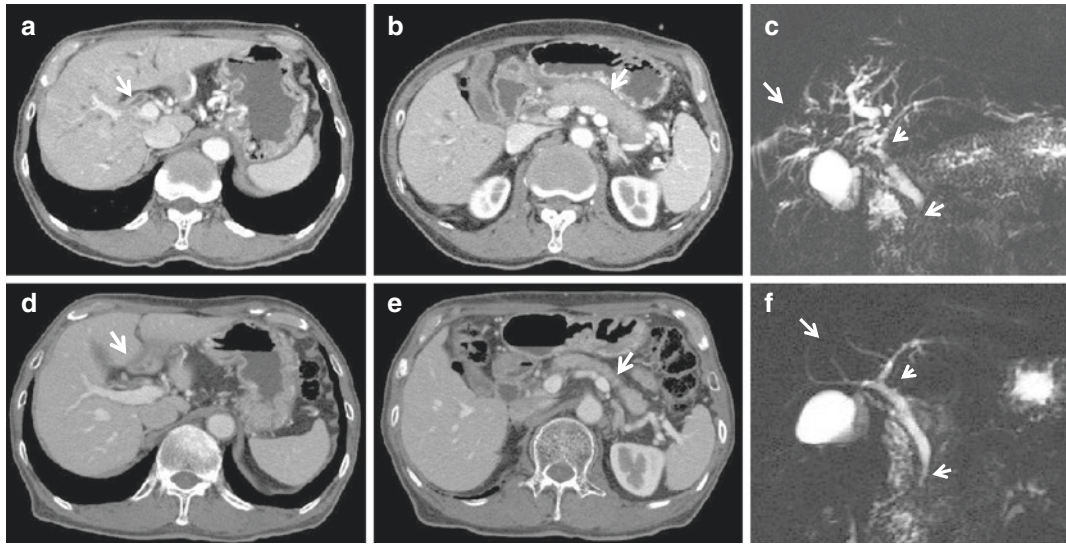

Fig. 8.3 A case of IgG4-SC complicated with AIP: CT showed the wall thickness of the hilar bile duct (**a**) and diffuse pancreatic swelling with capsule-like rim (**b**). MRCP displayed the stenosis of hilar, intrahepatic duct, and lower common bile duct (**c**). After steroid therapy, improvement of the imaging features was shown in (**d**) (bile duct wall thickness), (**e**) (pancreas swelling), and (**f**) (bile duct strictures)

IgG4-SC exhibited the following findings significantly more frequently: (a) wall thickening alone, (b) concentric wall thickening, (c) smooth inner margins, (d) homogeneous attenuation in the arterial phase, (e) a lesion involving the intrapancreatic bile duct, (f) smooth outer margins, (g) fully visible lumen, (h) a funnel-shaped proximal bile duct, (i) skip lesions, and (j) abnormal pancreatic findings. Conversely, (k) dual-layered attenuation in all phases was significantly more common in EH-CC [2].

Furthermore, they demonstrated that the following parameters demonstrated sensitivity values for diagnosing IgG4-SC of >80%: (c) concentric wall thickening, (j) abnormal pancreatic findings, (k) single-layered contrast enhancement in all phases,

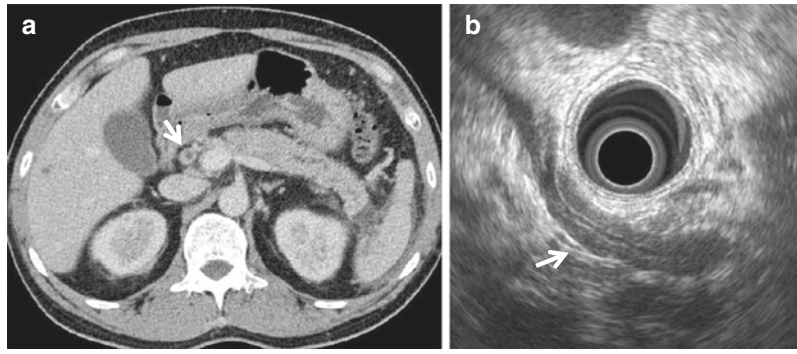

Fig. 8.4 A case of IgG4-SC with no biliary stricture but severe thickening of the bile duct wall [11]. Contrast-enhanced computed tomography revealed diffuse swelling of the pancreatic body and tail with a capsule like a low-density rim around the edge of the lesion and wall thickening with contrast enhancement in the region from the upper to the lower common bile duct with delayed enhancement (**a**); however, no stenosis of the bile duct was detected on MRCP. Obvious diffuse wall thickening of the common bile duct, which measured up to 4.0 mm in diameter, was observed on endoscopic ultrasonography (EUS) (**b**)

and (l) homogeneous attenuation in the delayed phase [2]. In addition, the following parameters exhibited specificity values for diagnosing IgG4-SC of >80%: (a) a lesion involving the intrapancreatic bile duct, (d) smooth outer margins, (e) a fully visible lumen, (g) funnel-shaped proximal bile ducts, (i) skip lesions, and (j) abnormal pancreatic findings [2]. Of the parameters mentioned above, only (j) abnormal pancreatic findings demonstrated both high sensitivity and specificity values.

Arikawa S et al. previously compared the CT findings between cases of sclerosing cholangitis with autoimmune pancreatitis (SC-AIP, n = 13) and EH-CC (n = 16) retrospectively [12]. Stricture length, stricture wall thickness, and proximal duct diameter were significantly smaller for SC-AIP than for EH-CCA, 19.3 ± 8.7 vs. 31.8 ± 12.0 mm (P = 0.004), 2.1 ± 1.3 vs. 4.1 ± 1.3 mm (P < 0.001), and 9.2 ± 3.9 vs. 13.3 ± 5.0 mm (P = 0.012), respectively [12]. SC-AIP was correlated with stricture location in both the intrapancreatic and hilar hepatic bile ducts, concentric stricture contour (P < 0.001), and diffuse concentric thickening of the proximal bile duct (P = 0.010) [12].

Kim JH et al. compared findings at CT, endoscopic retrograde cholangiography (ERC), and magnetic resonance cholangiography (MRC) in patients with SC-AIP and periductal infiltrating cancer in the CBD [13] and obtained similar results described as above. In that study, bile duct changes at dynamic CT, ERC, and MRC were compared in 58 patients with SC-AIP and CBD involvement and 93 patients with periductal infiltrating CBD cancer [13]. With CT findings, SC-AIP was more frequently associated with intrapancreatic CBD involvement, thinner CBD walls, concentric wall thickening, smooth outer margins, and lower degrees of upstream ductal dilatation and contrast enhancement ($P \leq 0.05$) than CBD cancer [13]. Maeda E et al. retrospectively assessed the CT findings of 22 patients with SC-AIP and 45 patients with EHCC and presented that EHCC was significantly more frequently associated with biliary obstruction (P = 0.0037), shorter lengths of the biliary lesions (P = 0.0036), and masses (P < 0.001) compared with SC-AIP [14].

In a while, Kim et al. [15] compared CT and MRI findings in 28 SC-AIP patients and 23 PSC patients and presented that on CT and MRI, the bile duct wall was thicker (5.1 vs. 3.1 mm, P = 0.033, and 4.3 vs. 3.0 mm, P = 0.01, respectively) in SC-AIP than in PSC patients. PSC was more frequently associated with intrahepatic bile duct wall thickening on both CT (93% vs. 50%; P = 0.024) and MRI (100% vs. 50%; P = 0.023) than SC-AIP.

Conclusion

Abdominal US can be useful for screening of the disease noninvasively. CT can be noninvasive and useful modalities for diagnose IgG4-SC. From the previous studies as above, we could obtain a number of CT findings to be useful for differentiating between IgG4-SC, PSC, and CC; however, there still exists several limitations in those studies including retrospective study and consensus reader analysis [2]. For an accurate diagnosis of IgG4-SC before steroid therapy, more detailed analysis should be required to develop a diagnostic system with other modalities and histological examinations.

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9 Imaging: MRI with MRCP

Jae Ho Byun

Introduction

The cholangiographic findings of IgG4-related sclerosing cholangitis (IgG4-SC) are heterogeneous and can mimic other biliary diseases, making it difficult to diagnose IgG4-SC on the basis of biliary changes on cholangiography alone [1–3]. MRI with MR cholangiopancreatography (MRCP) can simultaneously provide imaging of wall thickening of the bile ducts and its enhancement patterns, the pattern and degree of biliary strictures, and other IgG4-related disease in different intra-abdominal organs, such as autoimmune pancreatitis, IgG4-related renal disease, and retroperitoneal fibrosis [4]. Therefore, MRI with MRCP is a useful noninvasive diagnostic tool for IgG4-SC.

Cross-Sectional MR Imaging

The main finding of IgG4-SC on cross-sectional MRI is focal or diffuse wall thickening of the bile ducts, mostly associated with stenosis and mild dilatation of the upstream bile ducts [1, 5, 6]. The mean and median thicknesses of the involved common bile ducts are reported as 3 mm (standard deviation, 1.47 mm) and 4.3 mm (range, 2.5–9.7 mm), respectively [1, 5]. The involved thickened walls of the bile ducts are mostly concentric and homogeneously hypointense on T1-weighted images and isointense on T2-weighted images (88% and 75%, respectively) [1] (Fig. 9.1). In most cases, the thickened walls of the bile ducts are homogenously enhanced after administration of contrast materials (71.4–100%) and are iso- or hyperintense during the portal venous or delayed phases in comparison with adjacent hepatic parenchyma [1, 5, 6] (Fig. 9.1).

MR Cholangiopancreatography

The main feature of IgG4-SC on MRCP is the presence of focal or diffuse strictures in the bile ducts, which is one of the diagnostic criteria of IgG4-SC [4–8]. The most commonly involved location is the intrapancreatic common bile duct because of an association with simultaneous autoimmune pancreatitis in most cases [6, 9] (Fig. 9.2). In a recent retrospective study of 527 patients with IgG4-SC, intrapancreatic biliary strictures without any other strictures in the bile ducts were the most common finding (64%), followed by strictures in the biliary hilar portions (10%), both intrapancreatic and hilar portions (10%), and both intrahepatic and intrapancreatic portions (5–8%) [9] (Figs. 9.3 and 9.4). The

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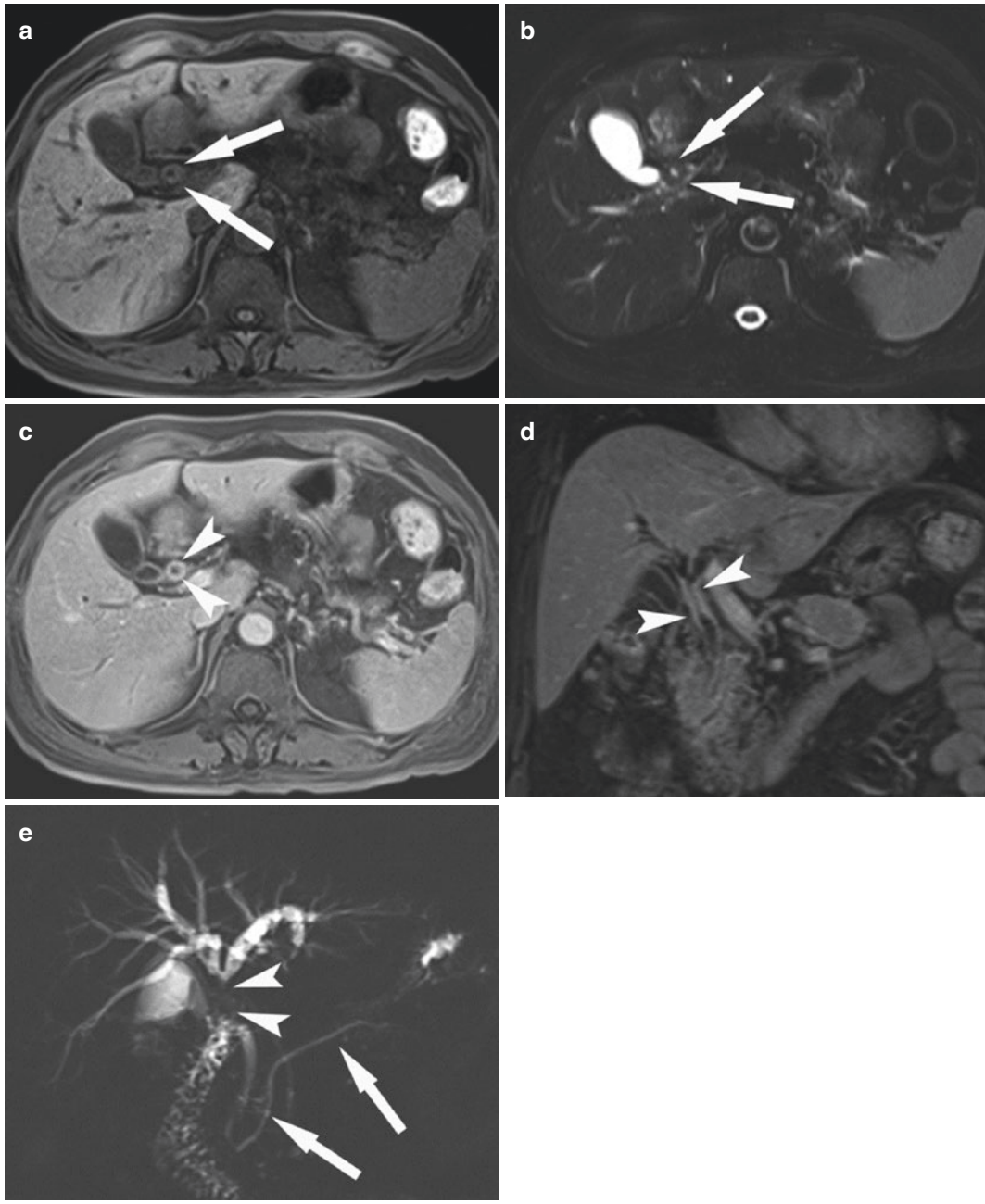

Fig. 9.1 IgG4-related sclerosing cholangitis. (**a**) T1-weighted axial image shows a concentric thickened wall of the proximal common ducts with hypointensity (arrows) in comparison with the hepatic parenchyma. (**b**) T2-weighted axial image shows a homogenously isointense thickened wall of the proximal common ducts (arrows) in comparison with the hepatic parenchyma. (**c**, **d**) Contrast-enhanced axial (**c**) and coronal (**d**) images show a segmental thickened wall of the proximal common ducts (arrowheads) with homogeneous enhancement. The wall thickening looks symmetric. The bile duct lumen in the involved segment is visible although narrowed. (**e**) MR cholangiopancreatography depicts a long stricture of the proximal common ducts (>2 cm in length; arrowheads) as well as dilated intrahepatic bile ducts which mimics the features of cholangiocarcinoma. In this case, the pancreatic duct (arrows) looks normal

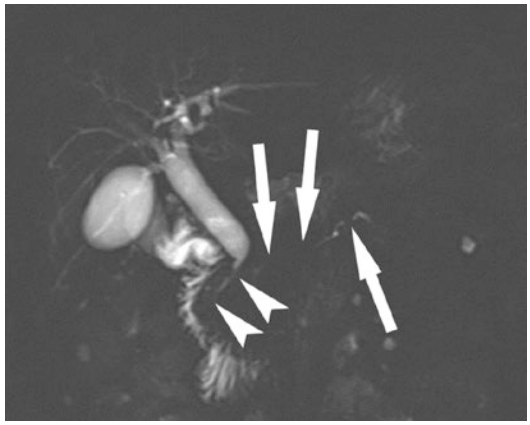

Fig. 9.2 IgG4-related sclerosing cholangitis and autoimmune pancreatitis. MR cholangiopancreatography demonstrates a long stricture of the distal common bile duct (>2 cm in length; arrowheads) with mild dilatation of the upstream bile ducts. Multiple segmental or long strictures of the pancreatic duct (arrows) without dilatation of the upstream pancreatic duct, a feature of autoimmune pancreatitis, are also seen

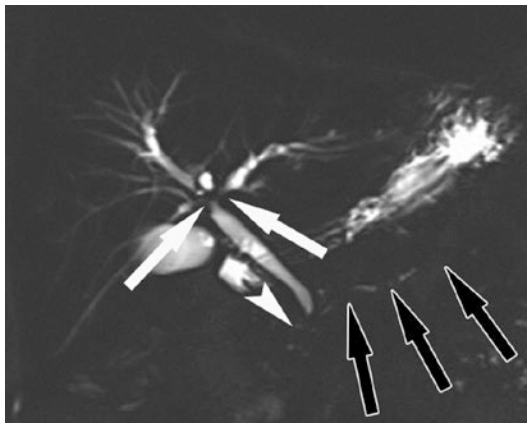

Fig. 9.3 IgG4-related sclerosing cholangitis and autoimmune pancreatitis. MR cholangiopancreatography shows a long stricture of the proximal left and right hepatic ducts and common hepatic ducts (white arrows). The distal common bile duct is also involved (arrowhead). The multiple strictures of the pancreatic duct (black arrows) are suggestive of autoimmune pancreatitis

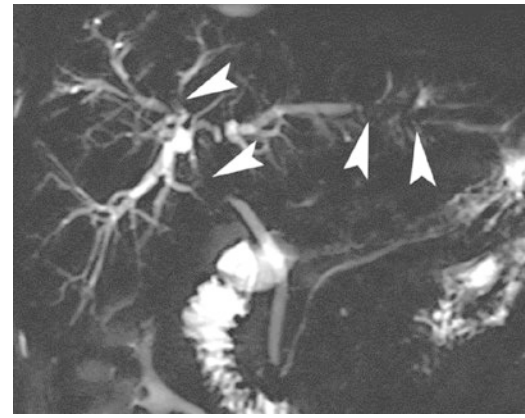

Fig. 9.4 IgG4-related sclerosing cholangitis. MR cholangiopancreatography shows multiple long or segmental strictures of both intrahepatic ducts, hilar portion of bile ducts, and proximal common ducts (arrowheads). In this case, the pancreatic duct looks normal

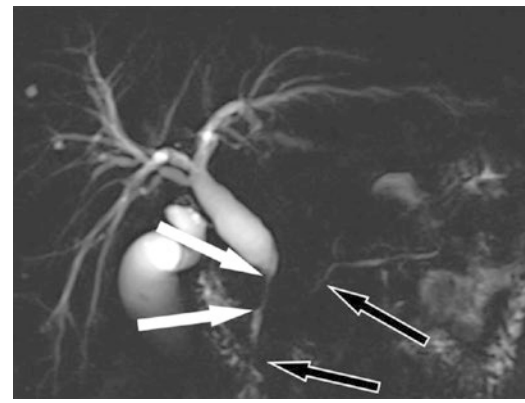

Fig. 9.5 IgG4-related sclerosing cholangitis and autoimmune pancreatitis. MR cholangiopancreatography shows a characteristic hourglass appearance in the involved common bile duct (white arrows), which indicates a smooth, symmetric, and gradual narrowing at both the proximal and distal ends of strictures with a fully visible lumen. A long stricture of the pancreatic duct (black arrows) without dilatation of the upstream pancreatic duct is also noted

lengths of biliary strictures are variable, focal (<3 mm), segmental (3–10 mm), or long (>10 mm) [1], although segmental or long biliary strictures are more common than focal strictures [2, 5, 10]. The strictures in the common bile ducts mostly show a smooth margin, gradual transition, and symmetry on MRCP (77.6–87.9%) [10]. A characteristic hourglass appearance in the involved common bile ducts, which indicates a smooth, symmetric, and gradual narrowing at both the proximal and distal ends of strictures with a fully visible lumen, is reported in 30.8% of cases of IgG4-SC of the common bile ducts on MRCP [10] (Fig. 9.5).

Other Organ Involvement in IgG4-Related Disease

The identification of IgG4-related disease in other intra-abdominal organs, one of the diagnostic criteria for IgG4-SC, is a very important clue in the diagnosis of IgG4-SC, allowing its differentiation from primary sclerosing cholangitis and cholangiocarcinoma [8, 11–13]. Therefore, MRI with MRCP, which can simultaneously show biliary strictures and pancreatic abnormalities, strictures of the main pancreatic duct, IgG4-related renal disease, and IgG4-related retroperitoneal fibrosis, is a very useful tool in the diagnosis of IgG4-SC. Accurate diagnosis of IgG4-SC in patients without other organ involvement is particularly difficult, as other biliary diseases may cause similar biliary changes on cholangiography.

On MRI with MRCP, the typical findings of the diffuse type of autoimmune pancreatitis are well known: diffuse enlargement of the pancreas, a capsule-like rim or halo around the pancreas, and diffuse or segmental irregular narrowing of the main pancreatic duct [4, 6] (Figs. 9.2, 9.3 and 9.5). The most common findings of IgG4-related renal disease are bilateral round or wedge-shaped peripheral cortical lesions with hypointensity on T2-weighted images, progressive enhancement (thus becoming indistinct as the phase passes) on contrast-enhanced T1-weighted images, and marked hyperintensity on diffusion-weighted images with high *b* values [6, 14, 15]. IgG4-related retroperitoneal fibrosis typically appears as a soft-tissue mass covering the abdominal aorta and its branches, or entrapping the ureters, and having variable signal intensity on T2-weighted images and variable enhancement on contrast-enhanced T1-weighted images, depending on the degree of active inflammation and maturity of the fibrous tissue [6, 7, 15].

Differential Diagnosis

Primary Sclerosing Cholangitis

On MRCP, primary sclerosing cholangitis (PSC) shows biliary changes that are the most difficult to distinguish from IgG4-SC with multiple biliary strictures, although the clinicopathological characteristics of both diseases are different from each other. MRI with MRCP findings that favor IgG4-SC over PSC include continuous involvement of the bile ducts instead of skip involvement, a thicker single-layer bile duct wall, diffuse wall thickening of the gallbladder, segmental or long strictures, and the presence of extrabiliary IgG4-related disease [1, 4–7, 16]. By contrast, those that favor PSC over IgG4-SC are focal stricture, multifocal and intrahepatic biliary stricture, and characteristic findings of PSC such as beaded, pruned tree, and diverticulum-like appearances [1, 4–7, 16].

Cholangiocarcinoma

IgG4-SC often mimics periductal infiltrating cholangiocarcinoma, particularly in cases with a single stricture in the hilar biliary portion or common bile duct. On MRI with MRCP, findings more likely to suggest IgG4-SC are multiple strictures with a smooth margin, gradual transition, symmetry, and hourglass appearance, and the presence of extrabiliary IgG4-related disease [4, 7, 10, 16]. By contrast, features favoring cholangiocarcinoma over IgG4-SC include a solitary lesion or stricture with irregular margins, abrupt transition, and asymmetry, indistinct outer margins, marked upstream biliary dilatation (>2 cm in diameter), the presence of an associated soft-tissue mass, and hyperenhancement relative to the hepatic parenchyma during the arterial or venous phases [4, 7, 10, 16].

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Imaging: ERCP

10

Atsushi Kanno, Atsushi Masamune, and Tooru Shimosegawa

Introduction

Further insights into autoimmune pancreatitis (AIP) have been revealed by many researchers since a report by Yoshida et al. in 1995 [1]. Bile duct stricture accompanied by AIP has been considered as IgG4-related sclerosing cholangitis (IgG4-SC) based on several reports [2, 3]. Recently, IgG4-SC is regarded as a manifestation of a systemic IgG4-related disease (IgG4-RD) [4]. The diagnosis of IgG4-SC is based on the clinical diagnostic criteria of IgG4-related sclerosing cholangitis 2012 [5]. The clinical symptoms of IgG4-SC are similar to those of AIP. IgG4-SC is often observed in patients aged 60 years or older; it is more common in males, is associated with elevated levels of serum IgG4, and responds well to steroids. A progressive course, such as that observed in cases of primary sclerosing cholangitis (PSC), is rare, and the short-term prognosis is extremely favorable. However, the long-term prognosis for IgG4-SC remains unclear. Accurate diagnosis of IgG4-SC is essential for proper management of this disease. We present bile duct images using endoscopic retrograde cholangiopancreatography (ERCP) in cases of IgG4-SC.

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Histopathological Features of IgG4-SC and PSC

To diagnose IgG4-SC on the basis of bile duct images, understanding of the histopathological features of the disease is essential. In cases of IgG4-SC, extensive thickening of the bile duct walls is noted, in addition to lymphocyte and IgG4-positive plasma cell infiltration, fibrosis, and obliterative phlebitis [6]. At times it can be difficult to distinguish between IgG4-SC and PSC.

On the other hand, PSC is a non-specific and chronic bile duct inflammation and fibrosis, characterized by narrowing, occlusion, or dilation of the bile duct. PSC can progress to cholestatic hepatocirrhosis. In addition, onion skin-like periductal fibrosis can be observed around the interlobular ductules, along with vanishing bile duct syndrome [7]. Bile duct findings on ERCP are reflected by these histopathological features.

Establishment of the Clinical Diagnostic Criteria of IgG4-Related Sclerosing Cholangitis 2012

Recently, IgG4-RD has been considered as a systemic disease. Comprehensive diagnostic criteria for IgG4-RD have been proposed for diagnosing several conditions [4]. According to these criteria, cases that do not fulfill the criteria for IgG4-RD must be diagnosed under the diagnostic

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criteria for each individual organ. For biliary manifestations of IgG4-RD, a research group from the Ministry of Health, Labour and Welfare and the Japan Biliary Association established the IgG4-SC diagnostic criteria [5]. According to these criteria, the diagnosis is made on the basis of the following factors: bile duct imaging findings, elevated serum IgG4 levels, IgG4-RD complications, concerning organs other than the bile ducts, and histological bile duct findings. Response to steroids was set as an optional factor similar to AIP. Therefore, comprehensive diagnosis on the basis of the clinical diagnostic criteria for IgG4-SC is important in addition to bile duct findings.

Bile Duct Images in Cases of IgG4-SC

Nakazawa et al. classified IgG4-SC into four categories (Fig. 10.1). Type 1 displays strictures in the lower part of the common bile duct that should be differentiated from the constrictions caused by pancreatic cancer or bile duct cancer. Type 2 displays strictures diffusely distributed not only in the

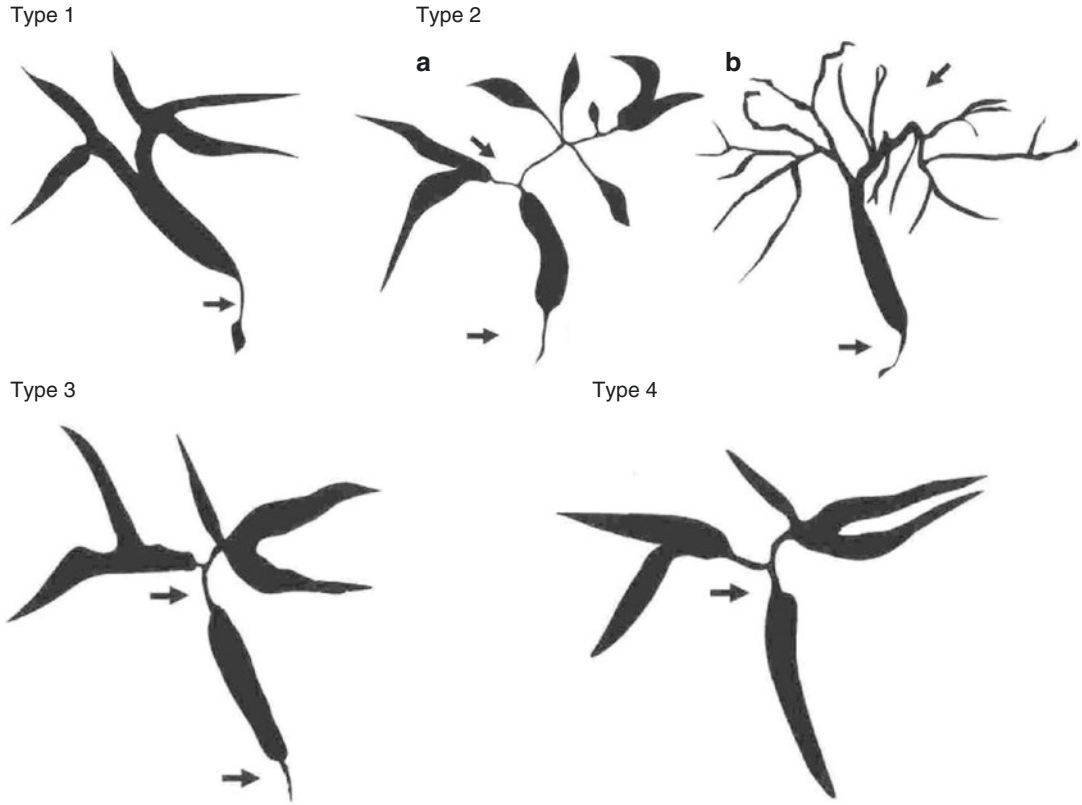

Fig. 10.1 Bile ducts affected by IgG4-related sclerosing cholangitis [8]. Type 1: Strictures only in the lower part of the common bile duct. This condition needs to be differentiated from pancreatic cancer. Type 2: Strictures are diffusely distributed in the lower part of the common bile duct and the intrahepatic bile ducts. This condition needs to be differentiated from primary sclerosing cholangitis. Type 2a is characterized by narrowing of the intrahepatic bile ducts with prestenotic dilation, and Type 2b is characterized by narrowing of the intrahepatic bile ducts without prestenotic dilation and reduced bile duct branches. Type 3: Strictures are displayed in the lower part of the common bile duct and the hepatic portal region. This condition needs to be differentiated from bile duct cancer. Type 4: Strictures are displayed only in the bile ducts of the hepatic portal region. This condition needs to be differentiated from bile duct cancer

lower part of the common bile duct but also in the intrahepatic bile ducts. These types can be further divided into two subtypes, both of which should be differentiated from PSC. Type 3 shows strictures in the perihilar and the lower part of the bile duct. Type 4 displays strictures only in the bile ducts of the perihilar region and should be differentiated from bile duct cancer. The differential diagnosis in each type of bile duct stricture should be performed by careful examination.

Distinguishing Between IgG4-SC and PSC

Characteristics of the bile duct strictures are different between PSC and IgG4-SC [8, 9]. Bile duct findings for PSC and IgG4-SC are shown in Fig. 10.2. The findings of bile duct images of PSC exhibit short band-like strictures (1–2 mm), a beaded appearance with short strictures and dilations alternately appearing, a pruned-tree appearance with reduced intrahepatic branching, and diverticulum-like outpouching. In contrast, bile duct findings of IgG4-SC are characterized by longer segmental strictures (3 mm or longer), long strictures with prestenotic dilatation (10 mm or longer), and strictures in the lower part of the common bile duct. It is important to accurately diagnose these bile duct findings. Strictures that occur with PSC are extremely stiff, and often a guidewire is not able to pass through the duct, despite contrast medium being able to flow to the liver side. In contrast, bile duct strictures of IgG4-SC are softer, and it is generally easier to pass a guidewire and to insert a bile duct stent. It is also important to consider this bile duct "hardness," observed during ERCP, for the diagnosis.

Distinguishing Between IgG4-SC and Bile Duct Cancer

In addition to PSC, bile duct cancer should be differentiated from IgG4-SC. According to the Nakazawa et al. classification scheme, Types 1

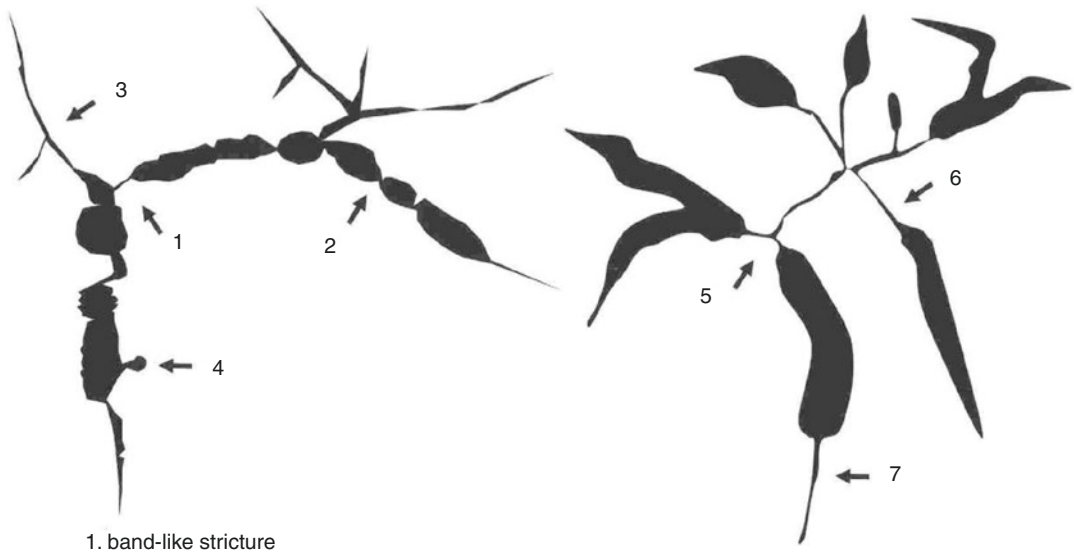

Fig. 10.2 Bile duct imaging characteristics in primary sclerosing cholangitis (PSC) and IgG4-related sclerosing cholangitis (IgG4-SC) [9]. 1–4 are specific to PSC, whereas 5–7 are characteristic of IgG4-SC

and 3 require differentiation from lower bile duct cancer, whereas Types 3 and 4 require differentiation from perihilar cholangiocarcinoma [4, 8]. Because most cases are very difficult to diagnose only on the basis of bile duct findings, it is important to consider factors that suggest the presence of IgG4-RD complications involving other organs, such as the pancreas, and whether or not the salivary glands are enlarged. The levels of serum IgG4 are also useful for differentiating between IgG4-SC and bile duct cancer. Ghazale et al. reported that elevated serum IgG4 levels were observed in 74% of 53 cases of IgG4-SC [3]. Nakazawa et al. also reported elevated IgG4 levels in 41 of the 47 cases they observed [10], suggesting that these findings are highly sensitive and specific. However, Ohara et al. reported an IgG4-SC cutoff level of 207 mg/dl for differentiating between IgG4-SC and bile duct cancer [11], indicating that the bile duct cancer with serum IgG4 ≥ 135 mg/dl may be misdiagnosed as IgG4-SC. Intraductal ultrasonography (IDUS) is useful for diagnosing IgG4-SC. Naitoh et al. reported the use of IDUS for differentiating IgG4-SC from bile duct cancer [12]. The bile duct wall thickening evidenced by IDUS in IgG4-SC and bile duct cancer is symmetrical and asymmetrical, respectively [12]. Kuwatani et al. reported that both IDUS and serum IgG4 should be used for diagnosing IgG4-SC and bile duct cancer [13]. It is important to diagnose on the basis of bile duct pathology; consequently, IgG4 immunostaining should be used in addition to hematoxylin and eosin staining for diagnosing IgG4-SC. Ghazale et al. reported the diagnostic yield of transpapillary bile duct biopsy to be 88% (14 of 16 cases) [3]. Kawakami et al. reported a high diagnostic performance of 52% (15 of 29 cases) [14]. However, the small sample volumes obtained from transpapillary bile duct biopsies make it difficult to identify obstructive phlebitis or storiform fibrosis. Naitoh et al. reported that only 18% of cases (3 of 17) could be accurately diagnosed with IgG4-SC after transpapillary bile duct biopsy [12], indicating that it is difficult to make an accurate diagnosis based solely on such a biopsy. Because there have been reports on the usefulness of liver biopsies [15–17] and the value of computed tomography (CT) scanning in differentiating IgG4-SC from bile duct cancer [18], it is important to use several modalities when diagnosing IgG4-SC.

Cases

Case 1 (Figs. 10.3 and 10.4)

The patient was a 66-year-old female, admitted to our hospital for examination of jaundice. An abdominal CT showed diffuse pancreatic swelling and bile duct dilatation. Her serum IgG4 level was 842 mg/dl. The findings of ERCP revealed a stricture in the lower part of the common bile duct. IDUS images showed symmetrical bile duct wall thickening. The patient was diagnosed with AIP complicated with IgG4-SC. Prednisolone (30 mg/day) was administered, and pancreatic swelling and the stricture in the lower part of the common bile duct improved after 1 month of treatment.

Case 2 (Figs. 10.5 and 10.6)

The patient was a 67-year-old male, referred to our hospital for examination of elevated levels of hepatobiliary enzymes and dilatation of the hilar bile duct. An abdominal CT showed swelling in the pancreatic tail and a stricture in the bile ducts in the perihilar portion. Serum IgG4 was high at 740 mg/dl and ERCP showed a perihilar bile duct stricture. IDUS images of the stricture showed symmetrical bile duct wall thickening and the histological findings of the bile duct were negative for malignancy. The patient was diagnosed as having AIP complicated with IgG4-SC. Treatment

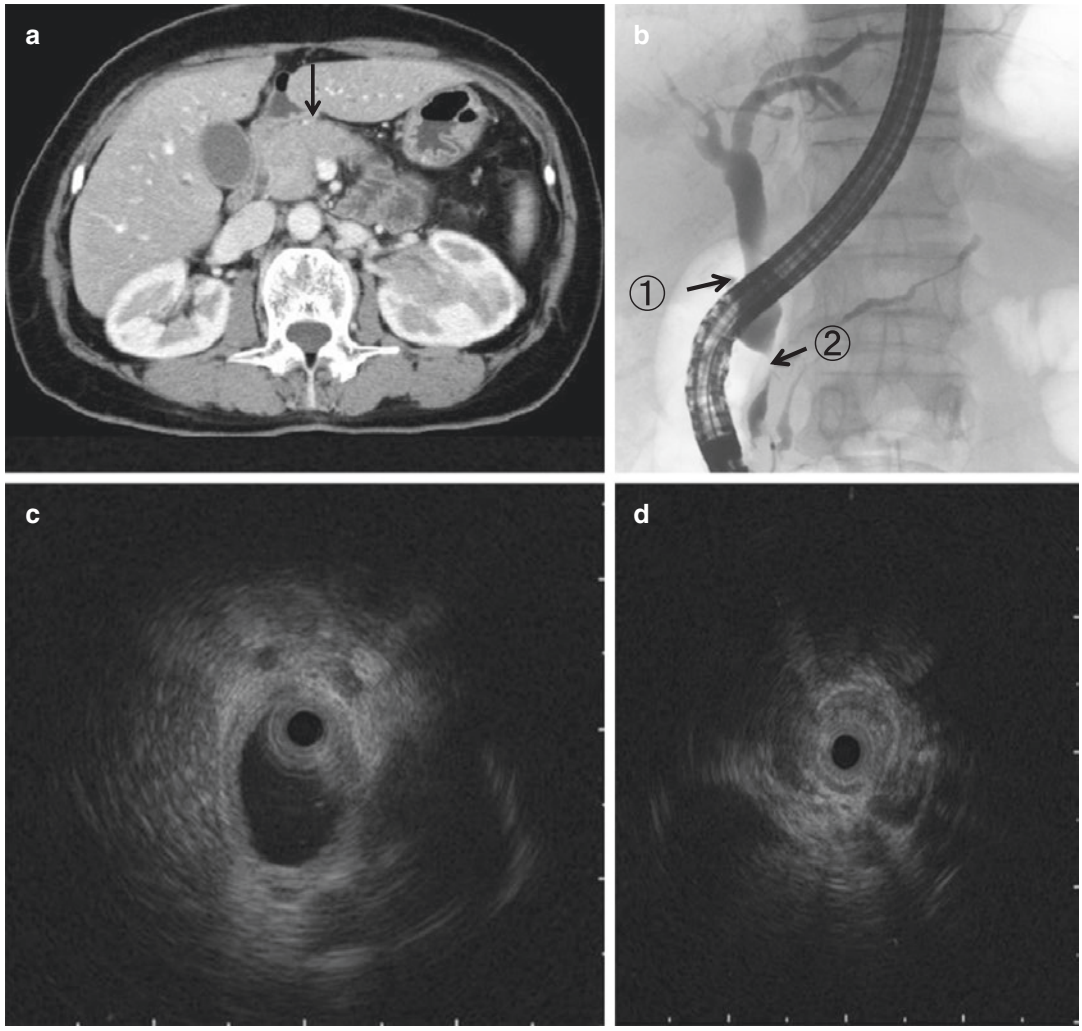

Fig. 10.3 IgG4-related sclerosing cholangitis with a stricture in the lower part of the common bile duct (case 1, pretreatment). (**a**) Abdominal computed tomography image showing pancreatic swelling (arrow). (**b**) Endoscopic retrograde cholangiopancreatography image showing a stricture in the lower part of the common bile duct (arrow 2). (**c**) Intraductal ultrasonography (IDUS) image (**b**, arrow 1) showing wall thickening outside a stricture. (**d**) IDUS image (**b**, arrow 2) showing asymmetrical wall thickening in a stricture

involved prednisolone (40 mg/day). The swelling in the pancreatic tail and perihilar bile duct stricture improved after 1 month.

We presented bile duct findings of IgG4-SC. Clinical diagnostic criteria for IgG4-SC enable better understanding of these diseases. There are many difficult cases to diagnose, such as cases of IgG4-negative IgG4-SC, IgG4-SC without AIP, or bile duct cancer with high serum IgG4 levels. We should diagnose these cases using bile duct findings, along with other modalities.

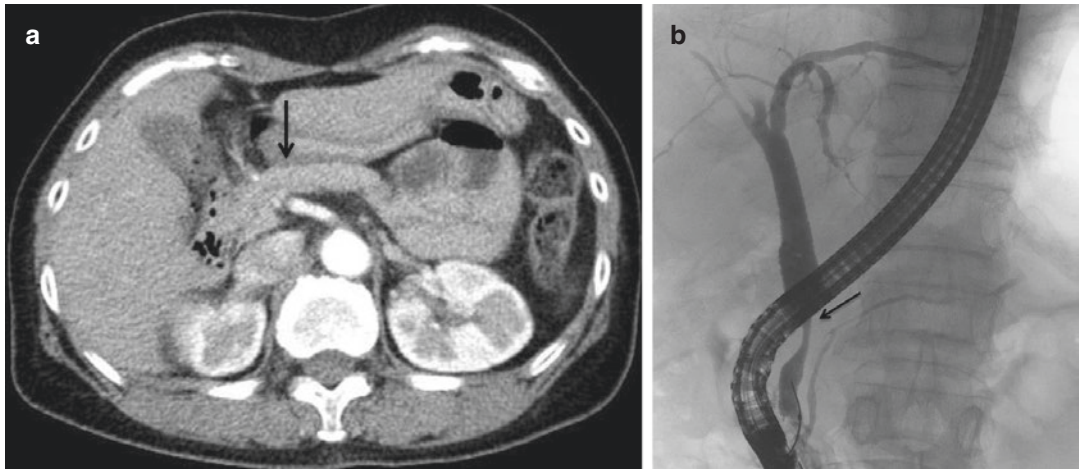

Fig. 10.4 IgG4-related sclerosing cholangitis with a stricture in the lower part of the common bile duct (case 1, posttreatment). (**a**) Abdominal computed tomography image showing an improvement in the pancreatic swelling (arrow). (**b**) Endoscopic retrograde cholangiopancreatography image showing an improvement in the stricture in the lower part of the common bile duct (arrow)

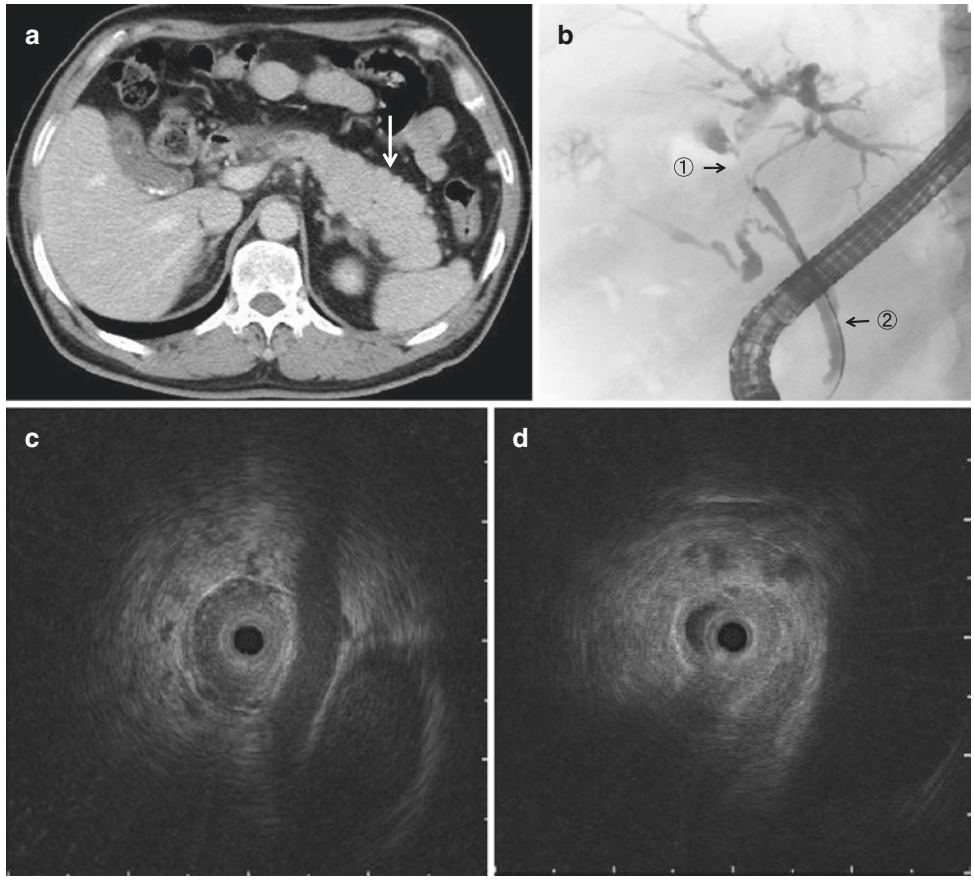

Fig. 10.5 IgG4-related sclerosing cholangitis with a stricture in a bile duct in the hepatic portal region (case 2, pretreatment). (**a**) Abdominal computed tomography image showing swelling in the pancreatic tail (arrow). (**b**) Endoscopic retrograde cholangiopancreatography image showing a stricture in a bile duct in the hepatic portal region (arrow 1). (**c**) Intraductal ultrasonography (IDUS) images (**b**, arrow 1) showing symmetrical wall thickening in the stricture. (**d**) IDUS images (**b**, arrow 2) showing asymmetrical wall thickening outside the stricture

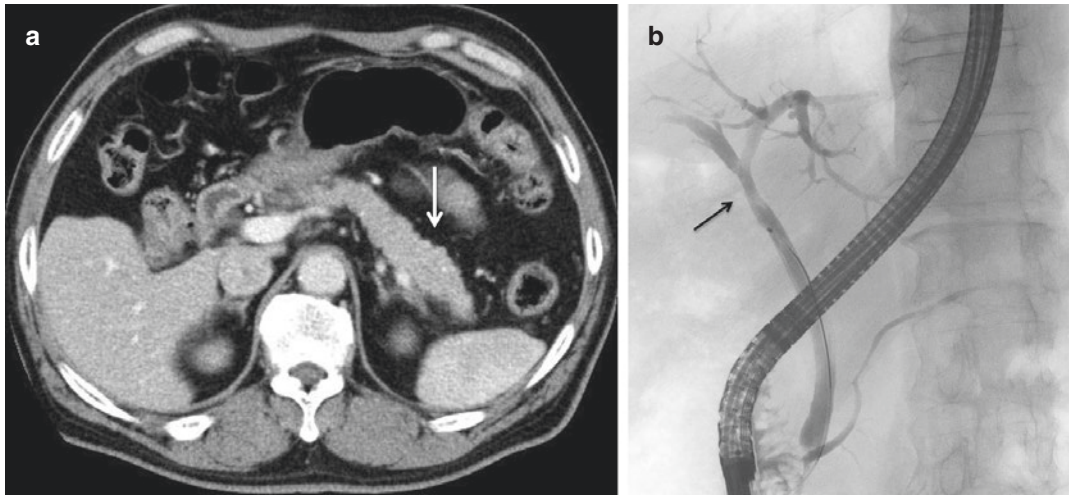

Fig. 10.6 IgG4-related sclerosing cholangitis with a stricture in a bile duct in the hepatic portal region (case 2, posttreatment). (**a**) Abdominal computed tomography image showing an improvement in the swelling in the pancreatic tail (arrow). (**b**) Endoscopic retrograde cholangiopancreatography image showing improvement in the stricture in the hepatic portal region (arrow)

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Imaging: EUS and IDUS

11

Itaru Naitoh, Takahiro Nakazawa, Hirotaka Ohara, and Takashi Joh

Endoscopic Ultrasonography (EUS)

Endoscopic ultrasonography (EUS) is a reliable diagnostic procedure that provides high-resolution images of nearby organs. Radial scanning and linear array EUS are used for the evaluation of pancreatobiliary diseases. Advanced EUS imaging, including EUS elastography and contrast-enhanced EUS, can be more useful than conventional EUS, which has only B-mode imaging abilities. EUS elastography is an imaging modality used for the evaluation of tissue stiffness and is also used for the differential diagnosis of solid pancreatic masses. Contrast-enhanced EUS uses a contrast agent and Doppler mode for vascularization imaging. Endoscopic ultrasonography-guided fine-needle aspiration (FNA) is now widely accepted as a safe and effective modality for histological evaluation of pancreatic tissue because of its high diagnostic accuracy and low complication rate.

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EUS Findings of IgG4-SC

No study has described the detection of IgG4-related sclerosing cholangitis (IgG4-SC) by EUS; however, several studies have evaluated the diagnostic ability of EUS for type 1 autoimmune pancreatitis (AIP). These type 1 AIP findings are important for the diagnosis of IgG4-SC, as most cases of IgG4-SC are associated with type 1 AIP [1]. The characteristic EUS finding for the diagnosis of type 1 AIP is diffuse hypoechoic pancreatic enlargement, sometimes with hyperechoic inclusions. Hoki et al. [2] compared conventional EUS findings between AIP and pancreatic cancer and determined that the incidences of diffuse hypoechoic areas, diffuse enlargement, bile duct wall thickening, and peripancreatic hypoechoic margins are higher for AIP than for pancreatic cancer. Hyodo [3] also reported marked wall thickening in the intrapancreatic common bile duct in all patients. Bile duct wall thickening is considered the EUS finding of IgG4-SC with type 1 AIP (Fig. 11.1).

Using conventional EUS imaging alone, some type 1 AIP cases can be difficult to differentiate from pancreatic cancer. Dietrich et al. [4] reported that EUS elastography of type 1 AIP shows a characteristic stiff elastographic pattern in not only the mass lesion but also in the surrounding pancreatic parenchyma. Hocke et al. [5] reported that type 1 AIP pancreatic parenchyma and the surrounding pancreas show hypervascularization, whereas the lesions of pancreatic cancer are hypovascularized

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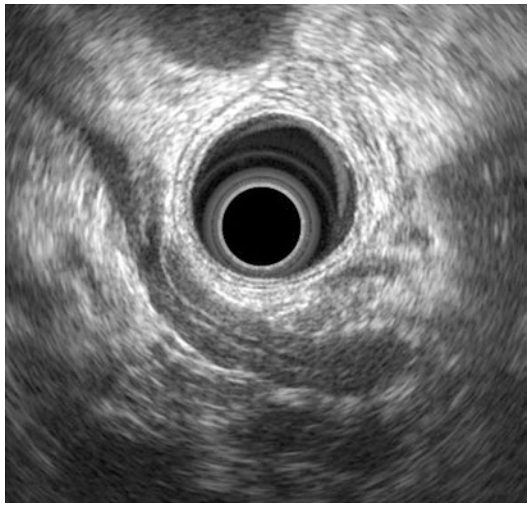

Fig. 11.1 Endoscopic ultrasonography shows diffuse wall thickening of common bile duct (CBD) in the patient with IgG4-related sclerosing cholangitis (IgG4-SC)

on contrast-enhanced EUS. Imazu et al. [6] used contrast-enhanced harmonic EUS to detect that the peak and maximum intensity gain of mass lesions in type 1 AIP were significantly higher than those of pancreatic cancer. Therefore, advanced EUS imaging techniques are useful tools for differentiating type 1 AIP from other pancreatic diseases.

Histological examination is critical for the definitive diagnosis of type 1 AIP. According to the International Consensus Diagnostic Criteria (ICDC), tissue samples obtained by EUS Trucut biopsy or surgical resection are considered suitable for the histopathological diagnosis of type 1 AIP, but EUS-FNA is not recommended, because it is difficult to obtain an adequate amount of tissue sample for histological evaluation. However, EUS-FNA using a 19-gauge needle has been reported to be useful for diagnosing type 1 AIP [7]. Kanno et al. [8] recently reported that EUS-FNA using a 22-gauge needle reliably provided a histological diagnosis of AIP, as determined by the ICDC, in 20 of 25 patients (80%). These findings suggest that EUS-FNA may provide new opportunities for the histological diagnosis of AIP.

The EUS finding of bile duct wall thickening suggests the presence of IgG4-SC with type 1 AIP. However, detailed images of bile duct wall thickening from EUS have not been reported. The coexistence of type 1 AIP is one of the diagnostic hallmarks for the ICDC diagnosis of IgG4-SC 2012 [9] and has a relatively high incidence. Therefore, the current role of EUS in the diagnosis of IgG4-SC is accurate diagnosis of type 1 AIP.

Intraductal Ultrasonography (IDUS)

After endoscopic retrograde cholangiopancreatography (ERCP), endoscopic transpapillary IDUS is another reliable procedure for the evaluation of bile duct wall thickening. IDUS is performed using a thin-caliber ultrasonic probe that consists of a sheath catheter, transducer, and cable. Biliary sphincterotomy is not necessary to perform this procedure using wire-guided IDUS. IDUS provides high-resolution images of the bile duct wall, which typically consists of inner hypoechoic and outer hyperechoic layers. With the development of optical technologies, IDUS can provide more detailed imagery of the bile duct, pancreatic duct, and adjacent structures. Bile duct wall thickness in patients with and without obstructive jaundice is typically reported to be less than 0.8 mm and 0.6 mm, respectively [10]. IDUS should be performed prior to biliary drainage because of mechanical inflammation that can occur following the procedure. IDUS is a useful modality for evaluation of bile duct stones, differential diagnosis of indeterminate biliary strictures, and superficial spread of bile duct cancer.

IDUS Findings of IgG4-SC

Characteristic biliary imaging findings are one of the four criteria for the clinical diagnosis of IgG4-SC 2012 [9]. Biliary tract imaging can reveal the characteristics associated with bile duct wall thickening, including diffuse or segmental narrowing of the intrahepatic and/or extrahepatic bile ducts. Computed tomography, magnetic resonance imaging, and EUS can also be used to detect bile duct wall thickness, but slight changes in thickness can be clearly observed using IDUS. Thus, IDUS is a useful modality for detailing bile duct wall thickening. IDUS findings of circular-symmetrical wall thickening, a smooth outer margin, a smooth inner margin, and homogeneous internal echo at the stenotic area are useful for the diagnosis of IgG4-SC (Fig. 11.2) [11–16]. The thickening of

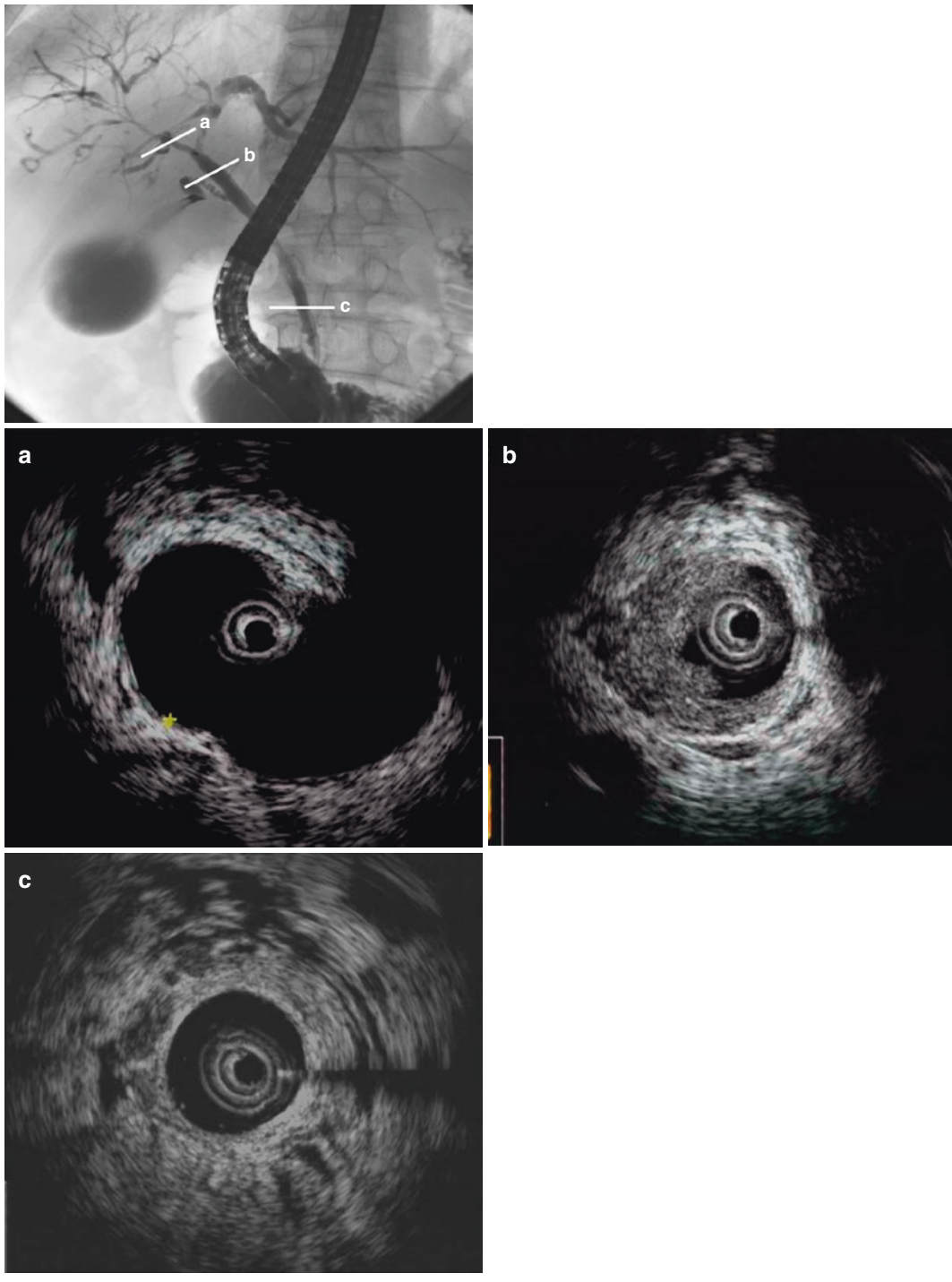

Fig. 11.2 Endoscopic retrograde cholangiography (ERC) shows intrahepatic stricture in the patients with IgG4-SC. (**a**) Intraductal ultrasonography (IDUS) shows wall thickness in the hilar stricture. Symmetry is circular-symmetric. Outer margin is smooth. Inner margin is smooth. Internal echo is homogeneous. (**b**) IDUS shows wall thickness in the middle CBD in which cholangiogram is normal. (**c**) IDUS shows wall thickness in intrapancreatic bile duct in which cholangiogram is normal

the bile duct wall, which appears normal on a cholangiogram, remains the most characteristic IDUS finding for the diagnosis of IgG4-SC. Bile duct wall thickening spreads continuously from the intrapancreatic bile duct to the upper bile duct in most IgG4-SC cases [11, 13, 17].

Comparison of IDUS Findings Between IgG4-SC and Cholangiocarcinoma (CCA)

Type 3 IgG4-SC is characterized by stenosis in the hilar hepatic lesions and the lower common bile duct, and type 4 IgG4-SC presents with bile duct strictures in the hilar hepatic lesions only. The cholangiographic findings of types 3 and 4 IgG4-SC should be differentiated from those associated with CCA. IDUS findings are different between IgG4-SC and CCA in each stricture and non-stricture lesion of the bile duct. IDUS findings for IgG4-SC include circular-symmetric wall thickness, a smooth outer margin, a smooth inner margin, and a homogeneous internal echo in the biliary stricture. For a CCA diagnosis, however, IDUS findings may consist of asymmetric wall thickness, a notched outer margin, a non-smooth inner margin, and homogeneous internal echo in the biliary stricture (Fig. 11.2). The most characteristic IDUS finding of IgG4-SC is wall thickness in non-strictures of the bile duct, which appears normal on a cholangiogram. Wall thickness continuously spreads from the intrapancreatic bile duct to the upper bile duct in most IgG4-SC cases. On the contrary, bile duct wall thickness is not observed in the non-stricture site with CCA because cancer is not present there (Fig. 11.2). According to receiver operating characteristic curve analysis, a bile duct wall thickness of 0.8 mm is the optimal cutoff for differentiating IgG4-SC from CCA, as this thickness appears normal on a cholangiogram. The sensitivity, specificity, and accuracy of IgG4-SC diagnosis using a bile duct wall thickness cutoff of 0.8 mm were 95%, 90.9%, and 93.5%, respectively. Using a cutoff of 1 mm, the sensitivity, specificity, and accuracy were 85%, 100%, and 87%, respectively. No CCA cases have been noted to have a bile duct wall thickness greater than 1 mm; therefore, this cutoff can be used to exclude CCA from IgG4-SC diagnoses completely [11]. A comparison of IDUS findings between IgG4-SC and CCA is summarized in Fig. 11.3.

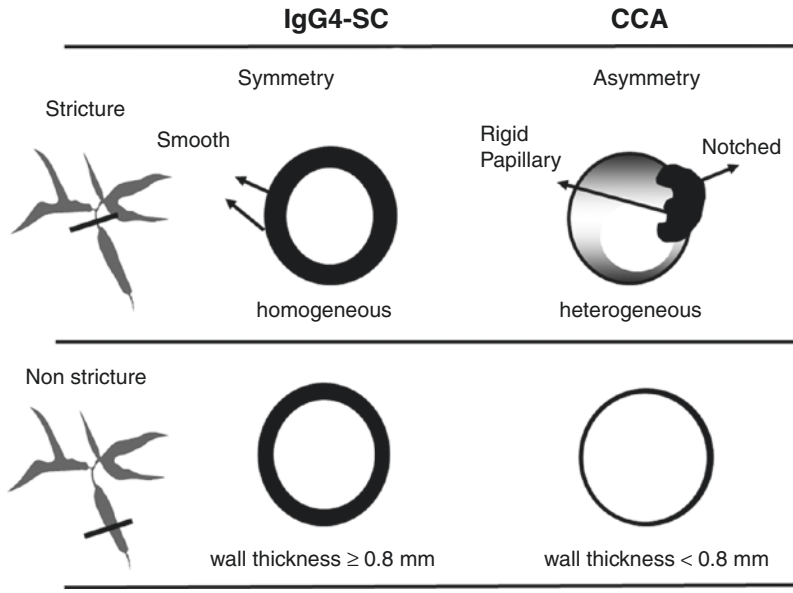

Fig. 11.3 Comparison of IDUS findings between IgG4-SC and CCA

IDUS Findings of Primary Sclerosing Cholangitis (PSC)

PSC is a chronic cholestatic liver disease of unknown cause characterized by chronic inflammation and obliterative fibrosis of the bile ducts, which leads to diffuse biliary stenosis and increased wall thickness throughout the intra- and extrahepatic bile duct. Type 2 IgG4-SC should be differentiated from PSC, because biliary stenosis is diffusely distributed throughout the intra- and extrahepatic bile ducts in both. Typical IDUS findings related to PSC include circular-asymmetric wall thickness, an irregular inner margin, an unclear outer margin, diverticulum-like outpouching, heterogeneous internal echo, and the disappearance of three layers (Fig. 11.4) [12, 18]. Kubota et al. [12] also observed asymmetric wall thickness and an unpreserved outer margin in stenotic lesions of the bile duct in patients with PSC. The specific ERCP findings for PSC are diverticulum-like outpouching, which is similar to band-like stricture, and a beaded or pruned-tree appearance. Diverticulum-like outpouching is considered to be the most objective finding on ERCP, but it has the lowest sensitivity of the specific findings for PSC. However, the sensitivity for detecting diverticulum-like outpouching is higher for IDUS than for ERCP in patients with PSC [18]. Therefore, IDUS is more useful than ERCP for the early detection of diverticulum-like outpouching, which is specific to PSC.

Comparison of IDUS Findings Between IgG4-SC and PSC

The thickening of the bile duct wall that spreads continuously from the intrapancreatic bile duct to the upper bile duct is observed in IgG4-SC and PSC. The incidences of circular-asymmetric wall thickness, an irregular inner margin, diverticulum-like outpouching, an unclear outer margin, heterogeneous internal echo, and the disappearance of three layers are higher in PSC than in IgG4-SC [18]. An irregular inner margin, diverticulum-like outpouching, and disappearance of three layers were specific IDUS findings for PSC, as compared with

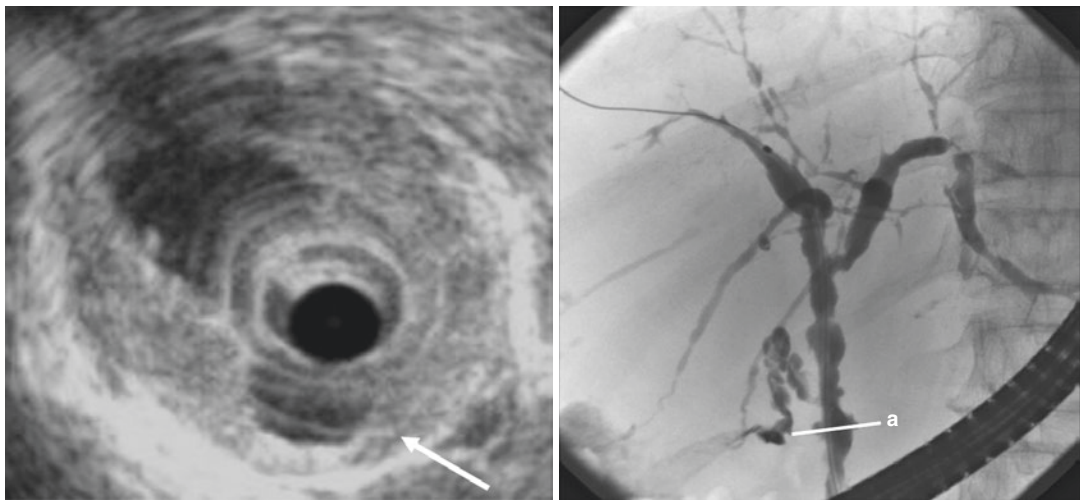

Fig. 11.4 ERC shows diverticulum-like outpouching in the patient with primary sclerosing cholangitis (PSC). (**a**) IDUS shows diverticulum-like outpouching (white arrow). Symmetry is circular-asymmetric. Inner margin is irregular. Outer margin is notched. Three layers were disappeared. Internal echo is heterogeneous, and internal foci are observed

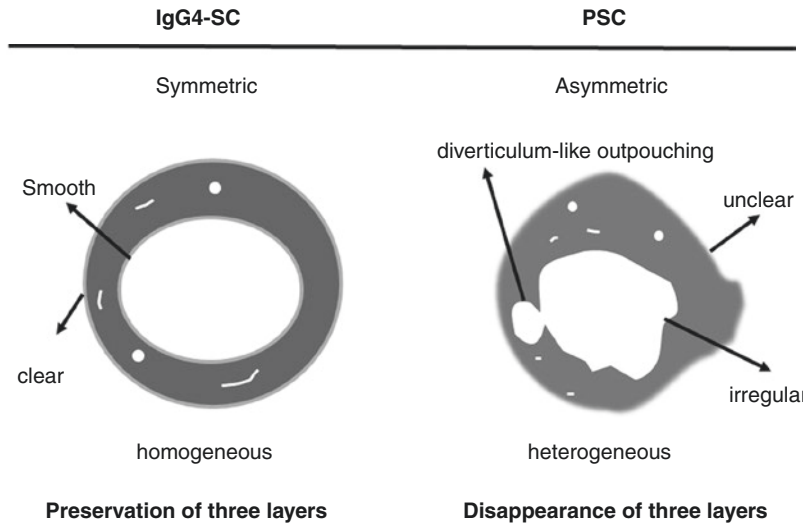

Fig. 11.5 Comparison of IDUS findings between IgG4-SC and PSC

IgG4-SC. Differences in IDUS findings between IgG4-SC and PSC clearly reflect pathological changes in the bile duct. Fibroinflammation is primarily observed in the stroma of the bile duct walls of patients with IgG4-SC, while the bile duct epithelium remains intact. The luminal side of the bile ducts, including the lining of biliary epithelial cells, is preferentially affected in patients with PSC. A comparison of the IDUS findings between IgG4-SC and PSC is summarized in Fig. 11.5.

Conclusions

EUS is important for the differential diagnosis of type 1 AIP from other pancreatic diseases and is useful for the diagnosis of IgG4-SC, which is often associated with type 1 AIP. CCA and PSC are important diagnoses that should be differentiated from IgG4-SC. IDUS findings of non-stricture bile duct lesions are different between IgG4-SC and CCA, and findings of stricture lesions vary between IgG4-SC and PSC. Therefore, IDUS is a useful modality for differentiating IgG4-SC from CCA and PSC, as the details of bile duct wall thickening are easily observable. Further EUS and IDUS improvements will ensure the appropriate and safe diagnosis of IgG4-SC.

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12 Differential Diagnosis from Primary Sclerosing Cholangitis

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Introduction

Primary sclerosing cholangitis (PSC), a chronic progressive disease of unknown etiology, is characterized by fibrosis and strictures involving the intra- and extrahepatic bile ducts [1, 2]. PSC is a distinct entity from IgG4-related sclerosing cholangitis (IgG4-SC), but some IgG4-SC masquerades as PSC by way of similar manifestations, such as frequent stenosis of both intra- and extrahepatic bile ducts, bile ductal wall thickening, male predominance, cholestatic liver dysfunction, and initial mild symptoms [3–7]. The differential diagnosis between PSC and IgG4-SC is clinically important because their treatment modalities and prognosis are very different [2, 7, 8]. Timely diagnosis of IgG4-SC can lead clinicians to prescribe adequate corticosteroid therapy that can reverse bile duct strictures/wall thickening and cholestatic liver dysfunction and could potentially prevent future advanced liver disease [2]. A proper diagnosis of PSC, in turn, is crucial for optimizing the surveillance of the disease progression to hepatic decompensation and the need for liver transplantation.

Interval screening for cholangiocarcinoma is also recommended for patients with PSC, because this disorder is associated with a lifetime risk of cholangiocarcinoma of around 7–14% [9]. The incidence of cholangiocarcinoma does not correlate with the duration of the PSC period, and approximately one-third of detected cholangiocarcinomas in PSC are identified within the first year of PSC diagnosis [10, 11]. A misclassification of PSC as IgG4-SC may result in inadvertent corticosteroid treatment and delay of the optimal surveillance, whereas a misclassification of IgG4-SC as PSC may result in missing the window for the steroid treatment and subsequent reversal of the disease progression. Discernment of the differences in the features of IgG4-SC versus PSC is therefore essential.

Differentiation by Clinical Features

Age

Age of presentation is a very important factor for differentiation between IgG4-SC and PSC (Table 12.1). PSC tends to be a disease of young adult and middle-aged persons, whereas IgG4-SC tends to be a disease of the elderly. The median age at diagnosis ranged from 35 to 45 years in patients with PSC [2, 7, 10, 12, 13], whereas this

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Table 12.1 Important points for differentiating between PSC and IgG4-SC

	Favor PSC	Favor IgG4-SC
Age	<40 years[a]	>60 years
Inflammatory bowel disease	Presence[a]	–
Serum IgG4	<140 mg/dL	>560 mg/dL[a]
Serum IgG4:IgG1 ratio[b]	<0.24	>0.24
pANCA	Positive	–
Association with autoimmune pancreatitis/IgG4-related disease	–	Presence[a]
Cholangiogram	Beaded appearance, diverticulum-like outpouching, pruned tree appearance	Longer stricture and more prestenotic dilatation, distal CBD stricture
Cholangioscopy	Scarring and pseudodiverticula	Dilated and tortuous vessel
Intraductal ultrasonography	Irregular inner margin, disappearance of three layers	Symmetrically thickened wall with smooth margin
Histology and immunohistochemistry	Onion-skin fibrosis and periportal sclerosis, sometimes IgG4-positive cell infiltration	Dense and richly IgG4-postive lymphoplasmacytic infiltration, marked fibrosis with storiform pattern, and obliterative phlebitis
Tissue IgG4+:IgG+ plasma cell ratio	<0.40	>0.40 {with IgG4+ plasma cells >10/HPF (biopsy) or 50/HPF (resection)}
Steroid responsiveness[c]	–	Positive[a]

[a]Reported specificity >90%
[b]In the setting of serum IgG4 level between 140 and 280 mg/dL
[c]Defined by radiographic resolution or marked improvement in the bile duct strictures and wall thickening after steroid therapy

range was 60 to 70 years in patients with IgG4-SC [5, 7, 14]. Interestingly, very few cases of IgG4-SC have been reported in young adults less than 40 years of age [2, 5, 7, 15]. A Japanese PSC cohort showed a second age peak at 65 years, but the diagnosis of PSC is uncommon over the age of 60 years in most populations. Patients with sclerosing cholangitis who are under the age of 40 years and who have no evidence of secondary causes are almost always afflicted with PSC, whereas those aged more than 60 years favor an IgG4-SC diagnosis.

Gender is generally not helpful for differentiation, as both of these sclerosing cholangiopathies show male predominance. The ratio of male predominance is 1.5:1 in PSC and 4-7:1 in IgG4-SC [8].

Association with Inflammatory Bowel Disease

The ratio of association with inflammatory bowel disease (IBD) differs somewhat between Western and Eastern countries, which probably reflects the basic prevalence of IBD. IBD is associated with majority of PSC patients, at a ratio of 60–80% in Western countries and 30–50% in Japan and Korea [1, 2, 7, 16–18]. By contrast, IBD is seldom associated with IgG4-SC, at a ratio of 5% in Western countries and 0% in Japan and Korea [2, 5, 14, 15, 19]. Patients with sclerosing cholangitis of unknown origin may show a presence of IBD that favors the diagnosis of PSC rather than IgG4-SC, especially in the areas with a low prevalence of IBD.

Concurrent or History of IgG4-Related Disease

IgG4-SC lies within a spectrum of IgG4-related diseases, with the pancreas most commonly affected. IgG4-related pancreatitis, or so-called type 1 autoimmune pancreatitis (AIP), is commonly associated with the IgG4-SC patient population, at a ratio of 70–92% [2, 5, 15]. Although

other autoimmune conditions coexist, PSC is seldom associated with pancreatic involvement [20]. Patients with sclerosing cholangitis of unknown origin may have concurrent or a history of AIP-/IgG4-related disease that may lead directly to a diagnosis of IgG4-SC. In the clinical setting, when differentiating between IgG4-SC and PSC, a meticulous evaluation of extrabiliary manifestations of Ig4-related disease should be performed when reviewing computed tomography scans or magnetic resonance images.

Differentiation by Serology

Serum IgG4

Despite the disease nomenclature of "IgG4"-SC, the assessment of serum IgG4 in isolation does not straightforwardly differentiate IgG4-SC from PSC. Recent research has shown that 9–26% of patients with classic PSC had elevated serum IgG4 levels (>135 mg/dL or >140 mg/dL) [2, 7, 12, 21–24]. Among patients with IgG4-SC, 60–90% had elevated serum IgG4 levels [2, 5, 7, 8]. Application of a cutoff value for serum IgG4 of 560 mg/dL, which is four times the upper limit of normal (ULN), gives a specificity of 100% for IgG4-SC [21]. For mildly elevated serum IgG4 levels (1–2 × ULN), a ratio of serum IgG4/IgG1 > 0.24 might be helpful for the differentiation of PSC from IgG4-SC [21].

pANCA

The most prevalent autoantibody in PSC is a particular type of perinuclear anti-neutrophil cytoplasmic antibody (pANCA) [18]. This pANCA is not typically used for the diagnosis of PSC because it is not specific for PSC; it is also observed in ulcerative colitis and autoimmune hepatitis [1, 18]. However, pANCA may have a role in the differentiation of PSC from IgG4-SC because it is observed in 40–60% of patients with PSC but in less than 10% of patients with IgG4-SC [2, 8].

Differentiation by Imaging

Cholangiogram

Characteristic cholangiographic features might also allow differentiation between IgG4-SC and PSC. The typical cholangiographic features for PSC are a beaded appearance, diverticulum-like outpouching, and a pruned tree appearance [25, 26]. The distinctive cholangiographic features of IgG4-SC that differentiate it from PSC are a distal CBD stricture, longer stricture, and more prestenotic dilatation [25–27]. However, these cholangiographic features can be observer dependent. A blinded multicenter study by worldwide specialists revealed that the cholangiogram had a high specificity (88%), poor sensitivity (45%), and slight interobserver agreement (kappa 0.18) for the diagnosis of IgG4-SC [28]. This poor sensitivity of cholangiographic findings suggests that many patients with IgG4-SC may be misdiagnosed with PSC or cholangiocarcinoma if the cholangiogram is used in isolation for the diagnosis. Apart from cholangiography, an endobiliary biopsy should be routinely performed at the time of endoscopic retrograde cholangiopancreatography (ERCP), in the setting of obstructive jaundice/cholangitis or a dominant stricture.

Cholangioscopy/Intraductal Ultrasonography

Direct endoscopic visualization of the biliary tree may aid in the differentiation between PSC and IgG4-SC. Characteristic cholangioscopic features of PSC include scarring and pseudodiverticula, whereas dilated and tortuous vessels are characteristic in IgG4-SC [29]. These dilated and tortuous vessels in IgG4-SC can be differentiated from the tumor vessels of cholangiocarcinoma by assessment of the patterns of proliferative vessels [29].

The intraductal ultrasonographic findings also differ between IgG4-SC and PSC [30]. Irregular inner margins, diverticulum-like outpouching, and the disappearance of the three layers are specific intraductal ultrasonographic findings for

PSC, when compared with IgG4-SC [30]. By contrast, intraductal ultrasonography of IgG4-SC shows a symmetrically thickened bile duct wall with smooth margins and preservation of the three layers [30].

Differentiation by Histology

If a resected specimen is available, histologic differentiation is mostly possible. The characteristic features of PSC include onion-skin fibrosis and periportal sclerosis [8]. The surface epithelium of the thickened bile duct, when infiltrated by lymphoplasmacytes in PSC, is often inflamed and shows edema, sloughing, erosion, and neutrophilic infiltration [24]. By contrast, the transmural lymphocyte infiltration in IgG4-SC spares the biliary lining epithelium [24]. The characteristic features of IgG4-SC include dense and richly IgG4-postive lymphoplasmacytic infiltration, marked fibrosis with a storiform pattern, and obliterative phlebitis in accordance with type 1 AIP [24]. Recent research has revealed that liver explants from classic PSC show IgG4 positivity in 23% of the tissues [24]. A consensus statement on the pathology of IgG4-related disease stipulates >10/HPF as the cutoff for the number of IgG4+ plasma cells in pancreas and bile duct for biopsy and >50/HPF for surgical specimens [31]. Moreover, the ratio of IgG4+ to IgG+ plasma cell >40% is mandatory for histologic diagnosis of IgG4-related disease [31].

An endoscopic intraductal forceps biopsy obtained from the biliary stricture in most cases does mostly not show these histologic features due to its small sample size. Variable sensitivities of IgG4 immunostaining of an endobiliary biopsy for diagnosing IgG4-SC have been reported, ranging from 18 to 88% due to the small sample size and possible patchy involvement [5, 32–34]. IgG4 immunostaining of endobiliary biopsy specimens was positive for IgG4-SC patients, independently of the presence of elevated serum IgG4 levels [35]. However, IgG4 immunostaining of endobiliary biopsy specimens from patients with PSC also showed up to 18% positivity for tissue IgG4 [2, 33]. This tissue IgG4 positivity should therefore be viewed in conjunction with the entire clinical, imaging, and serological features of each individual patient.

Differentiation by Steroid Trial

The use of steroid responsiveness as a diagnostic tool may be important, as steroid responsiveness is the most distinguishing clinical feature between IgG4-SC and PSC [2]. Some researchers have argued that a small portion of patients with PSC show positive steroid responsiveness, but the positive steroid responsiveness of PSC is only an isolated biochemical response, especially in patients with overlap syndrome between PSC and autoimmune hepatitis [22, 36–38]. The resolution of biliary strictures following corticosteroid treatment alone is not observed in PSC, but is typically seen with IgG4-SC. The reversal of the biliary strictures of PSC can be obtained by balloon dilatation and/or biliary stenting [22]. For differentiation of IgG4-SC from PSC by a steroid trial (steroid use as a diagnostic trial), the definition of steroid responsiveness is of utmost importance. Positive steroid responsiveness can be defined as radiographic resolution or a marked improvement in the bile duct strictures and wall thickening in response to steroid therapy [2]. A biochemical response alone after steroid therapy should not be designated as a positive steroid responsiveness for the purposes of this differentiation.

Proposal of Strategy for Differentiation by Combination of Features

The interpretation of serum/tissue IgG4 and the cholangiographic and histologic features as a means of differentiating between IgG4-SC and PSC may occasionally require a substantial amount of experience by the clinician, especially when a serum/tissue IgG4 is elevated in a patient with presumed PSC or when IgG4 is normal in a

patient with presumed IgG4-SC. Our group has overcome this difficulty through the development of a simple scoring system for the discrimination of IgG4-SC from PSC that we can use in daily clinical practice [2]. The selected variables (estimated scores) include other organ involvement (yes, 3 points; no, 0 points), beaded appearance on cholangiography (yes, 0 points; no, 2 points), and age (<30 years, 0 points; 30–39 years, 1 point; 40–49 years, 2 points; 50–59 years, 3 points; ≥60 years, 4 points). The patients are classified, according to the sums of each score, into three categories: 0–4 points, probable PSC; 5–6 points, indicating a steroid trial; 7–9 points, probable IgG4-SC.

Our scoring system can be used as a basis for a clinical algorithm for patients with multifocal intrahepatic/hilar biliary strictures, with a focus on the differentiation between IgG4-SC and PSC (Fig. 12.1). The exclusion of cholangiocarcinoma is the step of utmost importance, because some imaging features of IgG4-SC overlap those of cholangiocarcinoma and because PSC is associated with a potential risk of cholangiocarcinoma. An endobiliary biopsy should be routinely performed at the time of ERCP in the setting of obstructive jaundice/cholangitis or dominant stricture. A liver biopsy can be performed in the presence of a tumefactive periductal nodule/mass. Serum CA 19-9 should be serially measured at baseline and during follow-up.

In the next stage of the evaluation, patients should undergo serum IgG4 measurement. If the serum IgG4 level shows an elevation greater than twofold, a steroid trial is indicated. If the serum IgG4 level is normal or shows an elevation of less than twofold, our scoring system is applied to these patients. For a steroid trial, prednisone 0.6–1.0 mg/kg (body weight) is administered for 2 weeks. Steroid responsiveness should be assessed based on follow-up imaging and the CA 19-9 level. When a steroid trial results in no response on imaging, an endobiliary/liver biopsy with IgG4 immunostaining could be considered. When the serum CA 19-9 rises even after biliary decompression, cholangiocarcinoma should be differentiated by means of a meticulous rebiopsy.

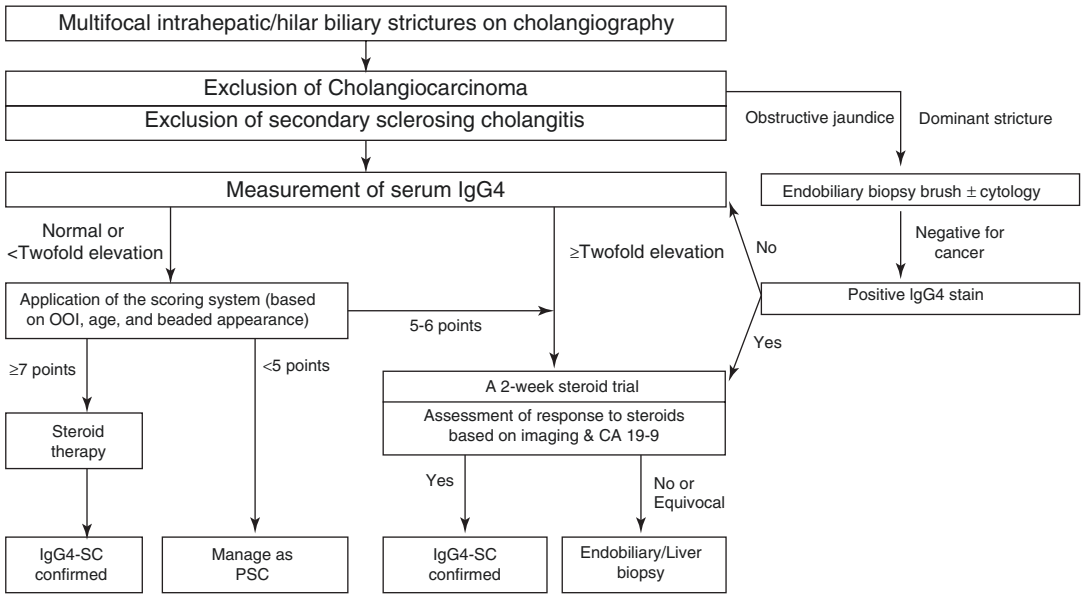

Fig. 12.1 Clinical algorithm for distinguishing IgG4-SC from PSC (adapted from J Gastroenterol 2017;52:483–493). OOI, other organ involvement (presence of IgG4-related extrabiliary lesions). The scoring system and the detailed description of algorithm are stated in the body text

Conclusion

Discernment of the differences between IgG4-SC and PSC is essential for clinicians. PSC tends to be a disease of young adult and middle-aged persons (median 35–45 years), whereas IgG4-SC is a disease of the elderly (median 60–70 years). The presence of IBD favors the diagnosis of PSC rather than IgG4-SC. A concurrent or history of AIP may lead to a straightforward diagnosis of IgG4-SC. Serum IgG4 is elevated in some patients with PSC; however, an elevation of more than 4x ULN is specific for IgG4-SC. Typical cholangiographic features for PSC include a beaded appearance, diverticulum-like outpouching, and a pruned tree appearance, whereas distinctive cholangiographic features of IgG4-SC, which differentiate it from PSC, are a distal CBD stricture, longer stricture, and more prestenotic dilatation. Tissue IgG4 should be interpreted in the appropriate clinical context on the basis of clinical features, imaging, and histopathological appearance. Positive steroid responsiveness is defined as radiographic resolution or a marked improvement in the bile duct strictures and wall thickening in response to steroid therapy. A correct diagnosis occasionally requires a constellation of multidisciplinary investigation.

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13 Differential Diagnosis Between Proximal-Type IgG4-Related Sclerosing Cholangitis and Hilar Cholangiocarcinoma

Kensuke Kubota, Akito Iwasaki, Takamitsu Sato, and Kunihiro Hosono

Introduction

IgG4-related sclerosing cholangitis (IgG4-SC) and Klatskin tumor are leading causes of indeterminate hilar biliary strictures (IHBS) and needed to differenciate from each other. Majority of IgG4-SC can be diagnosed without difficulty according to the JHBPS criterion 2012 [1] based on Nakazawa classification [2]. IgG4-SC patients are often associated with other organ involvements such as the pancreas (AIP), major salivary grounds, and/or retroperitoneal organs [1]. IgG4-SC can be divided into two types: the major is IgG4-SC associated with AIP (AIP-SC), and the minor is isolated IgG4-SC (i-SC). Moreover, i-SC consists of intrahepatic/hilar type (proximal, i-SC) and intrapancreatic type, and the characteristic features have been still unknown. Proximal-type IgG4-SC, especially Klatskin tumor mimicker, should be excluded because it could be controlled by steroid treatment; besides, Klatskin tumor would be treated by radical surgery or poor prognosis after conservative treatment [3]. Most proximal-type IgG4-SC are associated with AIP; on the other hand, i-SC is cumbersome to rule out cancer. Some proximal IgG4-SC developed as recurrence after remission of AIP. IgG4-SC affects deep lesion of mucosa beyond the epithelium with abundant IgG4-positive lymphoplasma cell infiltration with lateral lesion; besides, Klatskin tumor invades through the mucosa sometimes associated with skip lesion (Fig. 13.1). As endoscopic biopsy tried to detect cancer in the diagnosis of IgG4-SC, it could not evaluate and diagnose IgG4-SC because true lesion is located further in the deep lesion, in which biopsy forceps could not reach the lesion under the mucosa [4]. Steroid trial would be a better option under the situation [1]. This article showed the tips on how to differentiate from IgG4-SC and Klatskin tumor on the view points of imaging diagnosis and supplement role of steroid trial.

What Type of IgG4-SC Should Be Differentiated from Klatskin Tumor?

IgG4-SC can be classified into four types based on Nakazawa classification such as type 1 showing the bile duct stricture at the intrapancreas mimicking pancreatic head cancer and chronic pancreatitis, type 2 indicating stricture of the hilar part of the bile duct plus intrapancreatic bile duct stricture, being similar with primary sclerosing cholangitis (PSC), and types 3 and 4 showing strictures of hilar part of the bile duct with/without stricture in

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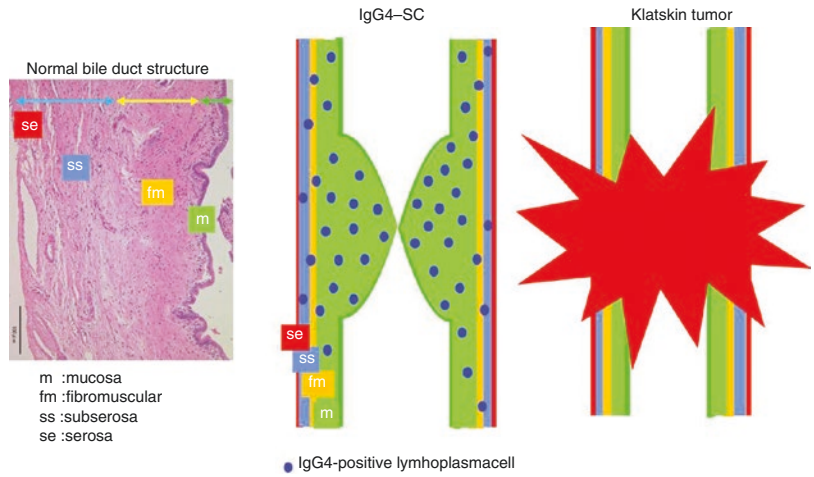

Fig. 13.1 Schema of IgG4-SC and Klatskin tumor based on histologic view of biliary mucosal structure. The main affected lesion in patients with IgG4-SC is under the mucosa [4, 6], which makes the long stricture of the bile duct. As the fibroinflammatory change showing IgG4-positive lymphoplasma cell infiltration is well noted in intestinal lesion of the bile duct, the surface of the epithelium of the mucosa is almost intact [4]. Besides, Klatskin tumor invade deep lesion of the bile duct over the mucosa [3]

the intrapancreatic bile duct [2]. Therefore, Klatskin tumor which affected the hilar part of the bile duct should be differentiated from IgG4-SC types 3 and 4 [1, 3, 4]. However, we have to bear in mind that some atypical patients with IgG4-SC is not always applied to the Nakazawa classification. Since majority of IgG4-SC would be associated with AIP and the diagnosis is facile, we should focus in diagnosis of cumbersome proximal-type i-SC. Distal type i-SC in pancreatic duct stricture was very rare, reporting only six cases in 2015 [5]. On the other hand, proximal-type i-SC has been reported in around 50 sporadic case reports. It comprised below 10% of all IgG4-SC. As there were only a few case report regarding IgG4-SC associated with cancer untill now, the malignant tendency of IgG4-SC was uncertain. For all these reasons, i-SC types 3 and 4 diseases or atypical i-SC should be aware in the diagnosis for indeterminant hilar biliary strictures.

Serological Marker

Serological markers such as IgG4 and CA19-9 in the different diagnosis from IgG4-SC and Klatskin tumor may be useful [1, 3]; however, a few studies for IgG4 and CA19-9 reveal regarding diagnosis between IgG4-SC and Klatskin tumor. Both IHBS were associated with jaundice. Carbohydrate antigen (CA) 19-9 levels do not always contribute in patients with obstructive jaundice; however, it may be acceptable after biliary drainage. An elevated IgG4 level suggests IgG4-SC [1, 6]. Nakazawa reported cutoff serum IgG4 level of 135 mg/dl did not contribute in the different diagnosis from IgG4-SC and cholangiocarcinoma [7]. Besides, Oseini et al. showed it would be the diagnostic if this IgG4 level set four holds in the different diagnosis under the situation with Klatskin tumor developed from PSC [8]. Nakazawa further studied that a cutoff level of 182 mg/dl enhanced the specificity to 96% in the different diagnosis from IgG4-SC types 3 and 4 and Klatskin tumor. In short, we should be aware for IgG4-SC in patients with IHBS showing serum IgG4 elevation with negativity for CA-19-9 level.

Fundamental Differences of Affected Lesion from IgG4-SC and Klatskin Tumor Based on Histopathology

It is important to get sufficient material to diagnose IgG4-SC because histopathology is the gold standard [1, 4, 6]. The main affected lesion in patients with IgG4-SC is under the mucosa such

as within the fibromuscular and/or subserous layer (Fig. 13.1). As the fibroinflammatory change showing IgG4-positive lymphoplasma cell infiltration is well noted in intestinal lesion of the bile duct, the surface of the epithelium of the mucosa is almost intact [4], but it often shows thickness of mucosa, which makes long stricture without obstruction (Fig. 13.1). These changes could be validated in cholangiography [2]. On the other hand, cancer developed from the bile duct mucosa and the tumor invaded to further deep layer longitudinally often associated with skip lesion to laterally [3]. Those differences give us tips for correct diagnosis; however, representative material for biopsy may not be obtained in IgG4-SC and cancer as well [3, 4, 9]. Although surgical resection is the lethal diagnostic tool, preoperative endoscopic biopsy may be a supplemental diagnosis for it. More often, insufficient endoscopic tissue acquisition would prevent determination of IgG4-SC [4, 9]. It is also difficult to reveal cancer cell prior to the surgical resection in patients with Klatskin tumor because when resection is undertaken with a presumptive diagnosis of hilar Klatskin tumor, a benign disease is identified in approximately 10% of cases including IgG4-SC [3]. For those cumbersome reasons, we could evaluate changes of mucosal lesions in imaging diagnosis and should know the limitation of endoscopic biopsy.

Ultrasonography (Abdominal US, EUS, and IDUS)

Although the images of abdominal ultrasonography, a noninvasive method, depend on operator's skill and patient condition, US (ultrasonography) partially depicts continuous and symmetrical thickening of the wall of the bile duct from hilar lesion in patients with IgG4-SC. It also detected the hypoechoic diffuse swollen pancreas like sausage shape without main pancreatic duct dilatation nor obstruction in AIP-SC [1]. Some pancreatic mass showed focal swollen pancreas in AIP-SC which made it difficult to discriminate from pancreatic cancer. Besides, those bile duct lesions were characterized layer by layer with hyperechoic lesion in patient with IgG4-SC, which could be detected by abdominal US and endoscopic ultrasonography (EUS) as well. Koyama et al. studied precise abdominal US features of two types of characteristic bile duct and gallbladder wall thickening, such as three-layer type, marked wall thickening apparent on US as high-low-high echo of the bile duct wall, and parenchymal-echo type, thickened wall that occupies the entire lumen of the bile duct with appearances of parenchymal echo in the bile duct, which were responded to steroid treatment [10]. They also pointed that abnormality of the biliary tract was recognized in 37.8% of the AIP patients [10]. EUS could enhance those findings including bile duct wall thickening in narrowed duct segments in detail. EUS and intraductal ultrasonography (IDUS) are more reliable for the diagnosis than abdominal US and staging for cancer and could detect symmetric wall thickening with smooth outer and inner margins associated with homogeneous internal echo, which spreads continuously from hilar to the intrapancreatic bile duct in patients with IgG4-SC (Fig. 13.2) [11, 12]. These lateral spreading findings detected by IDUS and EUS could be recognized in the bile duct wall which appeared also normal in cholangiogram [11]; however, Klatskin tumor often showed lateral spreading-type tumor which could mimic those features showed in patients with IgG4-SC [3].

CT and PET-CT

Proximal IgG4-SC shows similar biliary imaging features to Klatskin tumor, such as contrast enhancement of the bile duct wall in it. A contrast-enhanced CT depicts the affected lesion of the bile duct with mural thickening with early phase in the patients with IgG4-SC. These findings mimic Klatskin tumor. Recently, Yata et al. showed the usefulness of CT which indicated longer biliary lesion in IgG4-SC, and the dilated proximal intrahepatic bile duct was smaller in IgG4-SC than that with cancer [13]. As some IgG4-SC showed tumorous lesion in the affected hilar bile duct, the lesion of the bile duct is not completely obstructed in IgG4-SC (Fig. 13.1), which shows visible bile duct lumen target-like

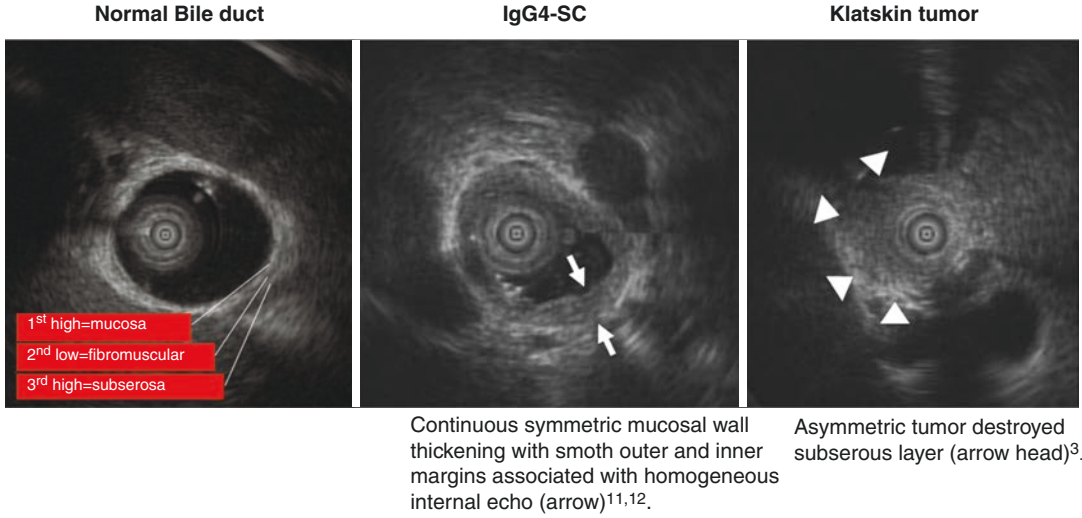

Fig. 13.2 IDUS findings of IgG4-SC and Klatskin tumor. In normal bile duct, a first high layer indicates mucosa. The second low shows fibromuscular lesion. The third high layer depicts subserosa. Continuous symmetric wall thickening with smooth outer and inner margins associated with homogeneous internal echo which spreads to hilar lesion in IgG4-SC [11, 12]. On the other hand, Klatskin tumor invades subserous layer [3, 17]

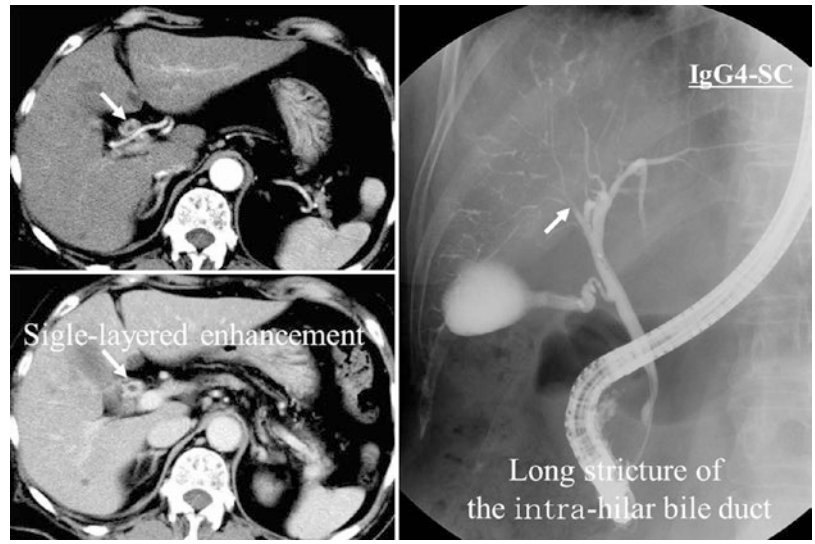

Fig. 13.3 Typical proximal-type IgG4-SC. CT shows single-layer enhancement of the bile duct like target lesion (arrow) [13]. Cholangiography shows long stricture on the intra-hilar part of the bile duct [2]

lesion of the bile duct (Fig. 13.3) [13]. They also revealed that visible bile duct lumen due to periductal infiltration of the lymphoplasma cells was more common in patients with IgG4-SC, which indicated as single-layered contrast enhancement. Regarding Klatskin tumor, dual-layered contrast enhancement of the bile duct wall was common (Fig. 13.4) [13]. As for PET-CT, some studies suggest that PET findings may change the treatment protocol in a small subset of patients with Klatskin tumor, but rarely does this occur in the absence of previous suspicious findings and/or an unexplained elevation in the CA 19-9 level [14]. However, PET-CT could detect concomitant extra-bile duct lesions such as the pancreas and retroperitoneal and/or salivary gland in patients with IgG4-SC. PET-CT can detect neoplasm and IgG4-SC, on the other hand,

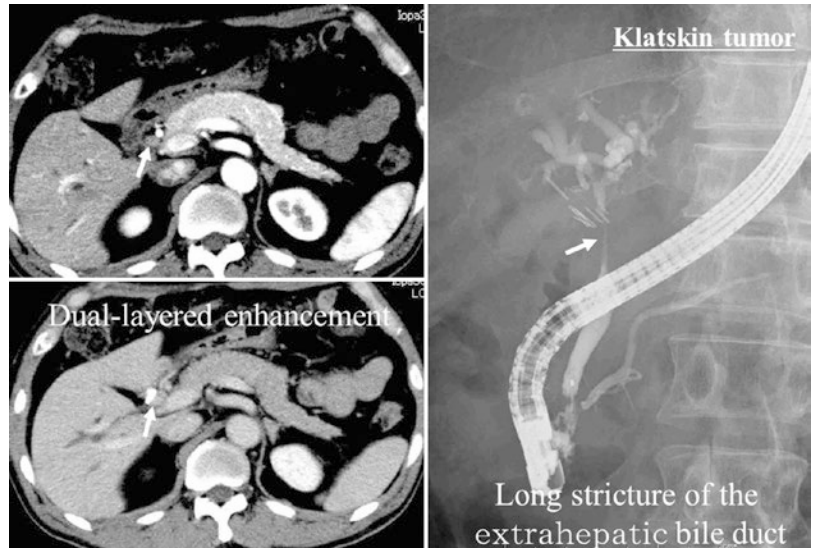

Fig. 13.4 Typical Klatskin tumor. CT indicates a faint double-layer enhancement of the bile duct [13]. Cholangiography shows obstruction of the bile duct

the intensity of PET would diminish corresponded to steroid treatment in patients with IgG4-SC.

ERCP and MRCP

The useful approach to the diagnosis for IgG4-SC is endoscopic procedures such as direct cholangiography, IDUS, and endoscopic biopsy to rule out cancer. Cholangiography is the fundamental method in the correct diagnosis for IgG4-SC. The dilatation after a long stricture of the bile duct is common in IgG4-SC [2, 15]. Nakazawa proposed a practical classification for IgG4-SC showing typical long stricture without dilation of short segmental stenosis (Fig. 13.2) [15]. Nakazawa types 3 and 4, showing stricture in the hilar part of the bile duct, should be differentiated from Klatskin tumor [2]. However, some atypical patients with IgG4-SC not applied to Nakazawa classification were sporadically reported. MRCP was mainly used in Western countries; besides, Asian stated that MRCP could not replace for direct cholangiography such as ERCP. It has often been difficult for MRCP to detect fine, slight long strictures seen in IgG4-SC. The affected lesion of the IgG4-SC could be visualized without being obstructed in direct cholangiography, which reveals the diagnostic image of IgG4-SC clear. Therefore, ERCP rather than MRCP would be appreciated as cholangiography. The segmental strictures which could not differentiate from IgG4-SC and cancer were encounterd. Those lesions are sometimes diagnosed as cancer and resected. When we encounter the long stricture of the hilar part of the bile duct with elevation of serum IgG4, we should always be aware of IgG4-SC [15].

POCS

POCS could give us direct intraductal mucosal images of the bile duct. The usefulness of small-caliber peroral video cholangioscopy (POCS) through mother scope in the different diagnosis from IgG4-SC and cholangiocarcinoma was reported. Itoi et al. studied in 33 pts.: IgG4-SC (n = 13), PSC (n = 5), hilar cholangiocarcinoma (n = 5), and distal cholangiocarcinoma (n = 10). They revealed that POCS detected the incidence of dilated or tortuous vessels and was significantly higher in IgG4-SC than that in Klatskin tumor, which would be cue for different diagnosis [16]. In contrast, the partially dilated vessels with encasement and fusion of vessels are more common to Klatskin tumor [16]. Those vascular abnormalities could make the different diagnosis more accurate.

Endoscopic Biopsy May Be Diagnostic for IgG4-SC to Exclude Malignancy?

Tissue acquisition was carried out using endoscopic forceps under fluoroscopic guidance for biliary mucosa and direct vision for ampulla of Vater. The biopsy specimens were stained with hematoxylin and eosin (H&E) and elastic van Gieson (EVG) if fibrosis was detected in it and conducted immunostaining for lymphoplasma cells with mouse antihuman IgG and IgG4 monoclonal antibody [4]. Only lymphoplasma cell infiltration could be evaluated in the endoscopic biopsy specimens. IgG4 positivity was defined as over 10 cell/high-power field (×400). IgG4/IgG ratio over 40% was regarded as positive [4, 6]. IgG4 immunostaining may provide histological support diagnosis for IgG4-SC. However, endoscopic biopsy itself could not rule out cancer completely and could not make a complete diagnosis for IgG4-SC as well. As endoscopic bile duct biopsy could get the intelligence of small and superficial bile duct mucosa and confusion with reactive atypia, it could not attest interstitial changes such as obliterative phlebitis and storiform fibrosis. Regarding brush cytology plus endoscopic biopsy in the diagnosis of Klatskin tumor, it provides fair results with a diagnostic sensitivity of 78% and a specificity of 100%, and these procedures should be repeated [17]. The diagnostic value of K-RAS mutation analysis, which is not specific for Klatskin tumor, has been tried in endobiliary brush cytology to detect malignancy [17]. Ghazale et al. showed the usefulness of endoscopic biopsy insisted that abundant IgG4-positive cells were well noted in biopsy material in patients with IgG4-SC [6]; however, Naito et al. [12] contradicted the usefulness of endoscopic biopsy for poor results, and they would rather use IDUS features in the diagnosis for IgG4-SC. As endoscopic biopsy could only reveal lymphoplasma cell infiltration with IgG4 positive, it might be supplemental diagnostic for IgG4-SC. Ampulla biopsy would be supplemental if IgG4-SC is affected in the lesion [1, 6, 11, 12]. Even though diagnostic endoscopic approaches have been used, the correct diagnosis for IHS continues to be challenging.

Steroid Trial as Correct Diagnosis

There were controversial issues regarding steroid trial in the diagnosis for IgG4-SC. IgG4-SC can be diagnosed based on a combination of biliary tract features, elevation of serum IgG4 levels, other organ involvements such as AIP, histological evidences taken from under the mucosal lesion, and an optional criterion of the steroid effectiveness [1]. It is not a tough work to diagnose AIP-SC; however, proximal isolated-type IgG4-SC would be cumbersome because its imaging diagnosis is hard to differentiate from Klatskin tumor. Additionally, endoscopic histopathological evidence would be lacked in both proximal-type IgG4-SC and Klatskin tumor [1, 3]. Under the situation, cases with IHBS with serum IgG4 elevation should be conducted in steroid trial [1]. Steroid administration was performed as treatment and also diagnosis as well [18]. Almost all patients with IgG4-SC are responded well to steroid treatment within 2 weeks after the administration, and the short duration of steroid trial is requisite to avoid misdiagnosis as cancer [1, 18]. However, some refractory IgG4-SC patients could not show quick responce to steroid treatment due to the irreversible fibrosis. Although imaging diagnosis has limitation, steroid trial sometimes would be appreciated. Therefore, negative workup for cancer is mandatory, and then steroid trial should be done carefully based on cholangiogram and serum IgG4 elevation [1].

Concluding Remarks

Imaging procedure plus serum IgG4 elevation has a pivotal and supplemental role in the different diagnosis for indeterminant hilar biliary strictures such as IgG4-SC and Klatskin tumor. Tips for imaging diagnosis were summarized in Table 13.1. Proximal isolated IgG4-SC is hard to diagnose. Steroid trial is one of the choices under the situation. Strategy for correct diagnosis using imaging diagnosis and steroid trial was indicated in Fig. 13.5.

Table 13.1 Different diagnosis using imaging diagnosis

Procedures	IgG4-related sclerosing cholangitis (IgG4-SC)	Klatskin tumor
Serum IgG4	>180–135 mg/dl [7]	<135 mg/dl [8]
Serum CA19-9	Almost within normal limits	Elevated [3]
US	Three-layer or parenchymal-echo type bile duct wall thickness [10]	Mass lesion in the bile duct [3]
EUS	Bile duct wall thickening in narrowed duct segments	Mass lesion in the bile duct [3]
IDUS	Continuous symmetric wall thickening with smooth outer and inner margins associated with homogeneous internal echo which spreads to hilar lesion [11, 12]	Mass lesion in the bile duct [3] (lateral-spreading type cancer mimic IgG4-SC)
CT	Single-layered enhancement (not obstructed completely) [13]	Dual-layered enhancement [13]
PET-CT	Positive and it decreased after steroid treatment	Positive
Cholangiography	Long stricture of the bile duct [2]	Segmental obstruction of the bile duct [3]
POCS	Dilated or tortuous vessels [16]	Partially dilated vessels with enhancement and fusion [16]
Endoscopic biopsy	Difficult to get sufficient material [12]	40–80% positivity for cancer [3, 17]
Steroid trial	Positive [1, 18]	Negative
Resected specimens	1. Lymphoplasmacytes infiltration and fibrosis [1, 7, 9]	Cancer cell
	2. IgG4-positive lymphoplasma cell infiltration [1, 7, 9]	
	3. Obliterative phlebitis [1, 7, 9]	
	4. Storiform fibrosis [1, 7, 9]	

IgG4-SC IgG4-related sclerosing cholangitis, *US* ultrasonography, *EUS* endoscopic ultrasonography, *IDUS* intraductal ultrasonography, *CT* computed tomography, *PET-CT* position-emission tomography in combination with computed tomography, *POSC* peroral video cholangioscopy

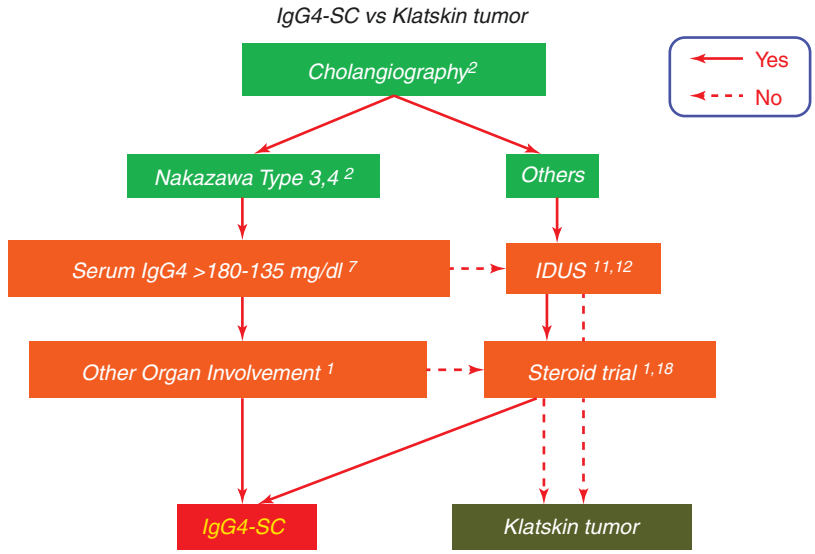

Fig. 13.5 Strategy for correct diagnosis using imaging modality and steroid trial. Cholangiogram in Nakazawa type 3 or 4 [2] plus serum IgG4 positivity and other organ involvement makes diagnosis for IgG4-SC [1]. Steroid trial [1, 18] should be done carefully in cases where atypical cholangiogram plus IDUS findings such as symmetric wall thickening with smooth outer and inner margins associated with homogeneous internal echo is noted [11, 12]

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14 Tissue Acquisition for Histologic Diagnosis

Ji Kon Ryu

Introduction

IgG4-related sclerosing cholangitis (IgG4-SC) is a characteristic sclerosing cholangitis with elevated serum IgG4 levels and dense infiltration of IgG4-positive plasma cells with extensive fibrosis in the bile duct wall [1]. IgG4-SC is now recognized as a spectrum of systemic IgG4-related disease. IgG4-SC is well resolved by steroid therapy which is a characteristic feature of IgG4-related disease. IgG4-SC is frequently associated with type 1 autoimmune pancreatitis (AIP), sialadenitis, and retroperitoneal fibrosis. However, some IgG4-SC cases do not involve any other organs. The cholangiographic abnormalities observed in IgG4-SC may resemble those of primary sclerosing cholangitis (PSC) and hilar cholangiocarcinoma. Because obstructive jaundice is frequently observed in IgG4-SC and IgG4-SC is most common in elderly men, the differential diagnosis with hilar cholangiocarcinoma is sometimes very difficult. Secondary sclerosing cholangitis also should be ruled out. Elevated serum IgG4 level is a characteristic feature of IgG4-SC and can suspect patients with IgG4-SC [2]. However, IgG4-SC cases without pancreatic involvement displayed no marked increase in serum IgG4 level compared with patients with AIP-associated IgG4-SC. There are two kinds of proposed diagnostic criteria for IgG4-SC. The one is the HISORt criteria, which were originally made for type 1 AIP, and the application was expanded to the IgG4-SC [3]. The other is the Japanese clinical diagnostic criteria which were proposed by the Japan Biliary Association in 2012 [4]. Japanese criteria were made by a combination of characteristic clinical, serological, morphological, and histopathological features with cholangiographic classification.

Indication for Tissue Acquisition

According to the Japanese criteria, histopathologic examination is always necessary for the definite diagnosis if there are no other organ involvements such as type 1 AIP, IgG4-related sialadenitis, and retroperitoneal fibrosis. Of course, probable diagnosis is possible without histopathologic evidence if the serum IgG4 level is elevated with effectiveness of steroid therapy. However, it is necessary to exclude a malignancy, PSC, and other secondary sclerosing cholangitis. So, histopathologic examination is also necessary to exclude other conditions. The characteristic features of IgG4-SC can be classified into four types based on the regions of stricture as revealed by cholangiography and differential diagnosis [5].

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Type 1 IgG4-SC shows stenosis only in the lower part of the common bile duct and often associated with type 1 AIP. This stricture might be caused by both the thickening of the bile duct wall and the effect of inflammation and/or edema of the pancreas. In such a typical case, tissue acquisition from the bile duct is not always necessary. However, tissue acquisition from the bile duct is usually recommended if there are strictures of hilar or intrahepatic bile duct (types 2, 3, and 4 IgG4-SC) not only for the definite diagnosis but also for the exclusion of other diseases.

Method of Tissue Acquisition

Endobiliary Biopsy

Endobiliary biopsy by endoscopic retrograde cholangiography (ERC) is a standard technique for tissue acquisition of the bile duct. Usually, endoscopic sphincterotomy is necessary for the insertion of biopsy forceps, and endobiliary biopsy by ERC is an invasive procedure. Under fluoroscopic guidance, the forceps is advanced to the level of the stricture and can grasp a specimen from the distal aspect of the stricture. The optimum number of biopsy specimens to obtain has not been established. Several studies suggested that at least three specimens should be obtained for the diagnosis of malignancy [6, 7]. Diagnostic yield of endobiliary biopsy is variable, and sensitivity for the diagnosis of malignancy is from 29% to 81% (average 60%) [8]. However, it is not easy to obtain sufficient bile duct tissue to study the characteristic histology of IgG4-SC biopsy specimens because fibroinflammatory involvement is observed mainly in the submucosa of the bile duct wall, whereas the epithelium of the bile duct is sometimes intact [9]. According to the Japanese criteria, histologic examination includes (1) marked lymphocytic and plasmacyte infiltration and fibrosis, (2) infiltration of IgG4-positive plasma cells: >10 IgG4-positive plasma cells/HPF, (3) storiform fibrosis, and (4) obliterative phlebitis. Especially, marked lymphocytic and plasmacyte infiltration and fibrosis and infiltration of IgG4-positive plasma cells are always necessary.

For better tissue acquisition, targeted biopsy in severe stricture site and multiple biopsies are recommended. Brush cytology can be performed for the diagnosis of cholangiocarcinoma if endobiliary biopsy is difficult in order to exclude a malignancy. Recently introduced method of visualizing the bile duct mucosa is direct peroral cholangioscopy (POC), using ultra-slim gastroscope. The video imaging can be obtained with POC, and targeted biopsy is possible with endobiliary biopsy forceps. Several studies reported that cholangioscopic finding which suggest malignancy are [1] irregularly dilated and tortuous vessels (tumor vessels), [2] easy oozing of blood, and [3] irregular surface (or papillary projections) [10, 11]. The SpyGlass direct visualization system (Boston Scientific) also allows for single-operator cholangioscopy (SOC). A new digital SpyGlass system has recently become available and can make cholangioscopy more accessible and useful. A SpyBite Biopsy Forceps (Boston Scientific) incorporates jaws at the tip designed to excise and retrieve visually targeted tissue. A systematic review of SpyGlass SOC studies reported that the pooled sensitivity and specificity of SOC-guided biopsy sampling in the diagnosis of malignancy were 60% and 98%, respectively [12]. However, there is no report of typical cholangioscopic finding of IgG4-SC, and the role of POC and SOC for the diagnosis of IgG4-SC is unknown.

Other Biopsy

Because inflammatory areas are usually localized to the outer portion of the bile duct, endobiliary biopsy is sometimes nondiagnostic. Ampullary biopsies are used as a surrogate marker for IgG4-SC even if the sensitivity is low. During ERC and endobiliary biopsy, performing ampullary biopsies is not difficult. So, routine ampullary biopsies can be recommended during ERC in patients with suspected IgG4-SC.

Liver biopsy can be useful and diagnostic if IgG4-SC involves intrahepatic small bile duct and be considered as a last tissue acquisition method if endobiliary biopsy is nondiagnostic.

Summary

IgG4-SC is a characteristic type of sclerosing cholangitis with increased serum IgG4 levels and dense infiltration of IgG4-positive plasma cells with extensive fibrosis in the bile duct wall. Histopathologic examination is always necessary for the definite diagnosis of IgG4-SC if there are no other organ involvements such as type 1 AIP, IgG4-related sialadenitis, or retroperitoneal fibrosis. The characteristic features of IgG4-SC can be classified into four types based on the regions of stricture as revealed by cholangiography and differential diagnosis. Endobiliary biopsy by ERC is a standard technique for tissue acquisition of the bile duct. However, it is not easy to obtain sufficient bile duct tissue to study the characteristic histology of IgG4-SC biopsy specimens because fibroinflammatory involvement is observed mainly in the submucosa of the bile duct wall, whereas the epithelium of the bile duct is sometimes intact. Recently introduced methods of visualizing the bile duct mucosa are direct POC, using ultra-slim gastroscope, and the SpyGlass direct visualization system. However, there is no report of cholangioscopic finding of IgG4-SC, and the role of POC and new digital SpyGlass system for the diagnosis of IgG4-SC is unknown. Liver biopsy can be useful and diagnostic if IgG4-SC involves intrahepatic small bile duct and be considered as a last tissue acquisition method if endobiliary biopsy is nondiagnostic.

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Other Organ Involvements

15

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Introduction

IgG4-related disease (IgG4-RD) is a fibroinflammatory disease that can involve essentially any organ simultaneously or metachronously [1]. It was first proposed as a systemic disease in 2003 by Kamisawa et al. following the recognition that a high percentage of patients with autoimmune pancreatitis (AIP) had extrapancreatic manifestations that shared similar histopathological features consisting of dense infiltration of IgG4-positive plasma cells and lymphocytes and fibrosis [2].

IgG4-related sclerosing cholangitis (IgG4-SC) is recognized as a biliary manifestation of IgG4-RD. Approximately 60% of IgG4-RD patients have IgG4-SC in the proximal and/or distal bile ducts [3]. Although there are diagnostic criteria for IgG4-SC, diagnosis of IgG4-SC remains a significant clinical challenge. Other organ involvements, such as AIP, might be helpful to diagnose IgG4-SC. In this chapter, we describe other organ involvements of IgG4-SC.

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Clinical Findings of IgG4-RD

IgG4-RD is a systematic disease that affects various organs, resulting in organomegaly or hypertrophy. Clinical symptoms depend on the pattern of each organ involvement and the severity of the disease activity. The course of IgG4-RD is varied. Some cases improve spontaneously, and the natural course of IgG4-RD is unknown [4]. IgG4-RD usually presents with a subacute onset, and a few cases of the disease lead to progressive organ failure. Although severe constitutional symptoms are rare, organomegaly or hypertrophy can sometimes cause serious complications of obstruction or compression including obstructive jaundice in AIP or IgG4-SC, visual disturbance in IgG4-related dacryoadenitis, and hydronephrosis in IgG4-related retroperitoneal fibrosis. Furthermore, persistent inflammation in affected organs has been shown to lead to fibrosis and permanent organ dysfunction or failure. Examples of such complications include exocrine and endocrine pancreatic dysfunction in AIP, liver fibrosis in IgG4-SC, and renal dysfunction in IgG4-related kidney disease [5].

Inoue et al. reported the incidence of IgG4-RD as follows. AIP is the leading manifestation of this systemic condition, being diagnosed in 60% of patients with IgG4-RD. The second most common manifestation is sialadenitis (34%), followed

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by tubulointerstitial nephritis (TIN) (23%), dacryoadenitis (23%), and periaortitis (20%) [6]. Multiorgan disease is easier to identify at diagnosis; however, organ disease may evolve metachronously, with one organ at a time becoming involved over months to years.

Essentially, all IgG4-RDs respond dramatically to steroids. Additionally, it has recently been reported that IgG4-RD is successfully treated with rituximab.

Diagnosis of IgG4-RD

The current gold standard for diagnosis of IgG4-RD is its characteristic histology, which consists of abundant infiltration of IgG4-positive plasma cells and lymphocytes and storiform fibrosis together with obliterative phlebitis. Almost all IgG4-RDs show similar histopathological features regardless of the organs involved, although fibrosis is rare in IgG4-related dacryoadenitis and IgG4-related lymphadenopathy.

Clinically, diagnosis relies on the coexistence of various clinical, laboratory, radiological, and histopathological findings. Other organ involvements and response to steroids may aid in diagnosis, although none of these findings by themselves are pathognomonic. IgG4-RD occurs predominantly in older males. Serum IgG4 levels are frequently and significantly elevated in patients with IgG4-RD. Computed tomography (CT), magnetic resonance imaging (MRI), and 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET) are common imaging methods used for diagnosis of other organ involvements of IgG4-RD. On enhanced CT images of IgG4-RD, diffuse or focal swelling of organs or soft tissue masses appears with soft tissue attenuation, well-defined margins, and homogeneous enhancement at the late stage. Accumulation of FDG is observed in almost all sites and organs affected by IgG4-RD.

Based on a combination of these findings, specific diagnostic criteria have been established for IgG4-RD in four organs: the bile duct (IgG4-SC) [7], pancreas (AIP) [8], kidney (IgG4-related kidney disease) [9], and lacrimal and salivary glands (IgG4-related sialadenitis and dacryoadenitis) [10]. In addition to these criteria, comprehensive diagnostic criteria for IgG4-RD have been proposed for practical use, which are independent of the predominant organ involvement (Table 15.1) [11].

Table 15.1 Comprehensive diagnostic criteria for IgG4-RD (2011) [11]

1. Clinical examination showing characteristic diffuse/localized swelling or masses in single or multiple organs
2. Hematological examination shows elevated serum IgG4 concentrations (≧135 mg/dl)
3. Histopathologic examination shows:
(a) Marked lymphocyte and plasmacyte infiltration and fibrosis
(b) Infiltration of IgG4 + plasma cells: ratio of IgG4+/IgG+ cells >40% and >10 IgG4 + plasma cells/HPF

1 + 2 + 3: definite
1 + 3: probable
1 + 2: possible

Other Organ Involvements of IgG4-SC

Autoimmune Pancreatitis

The pancreas was the first organ identified with IgG4-RD [2]. Of the two subtypes of AIP that are currently known, type 1 is the pancreatic manifestation of IgG4-RD, usually called AIP when referring to IgG4-RD. Type 2 AIP is characterized by granulocytic epithelial lesions [8].

On CT, typical AIP shows diffuse enlargement of the pancreas with delayed enhancement in association with a capsule-like low-density rim (Fig. 15.1). On endoscopic retrograde pancreatography, typical AIP shows diffuse irregular narrowing of the main pancreatic duct (Fig. 15.2). However, it is challenging to differentiate segmental-/focal-type AIP from pancreatic cancer. On pancreatography, long narrowing of the main pancreatic duct, skipped narrowed lesions, side branch derivation from the narrowed portion, and less upstream dilatation sug-

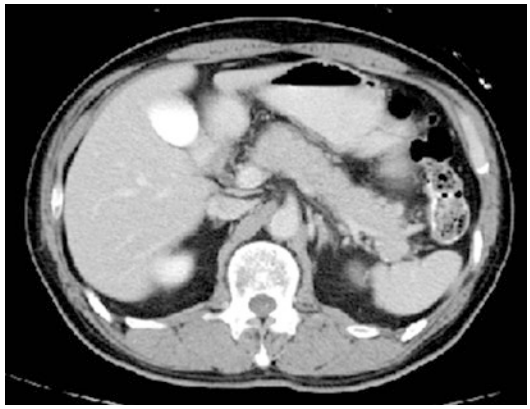

Fig. 15.1 Abdominal CT shows diffuse enlargement of the pancreas with delayed enhancement in association with a capsule-like low-density rim

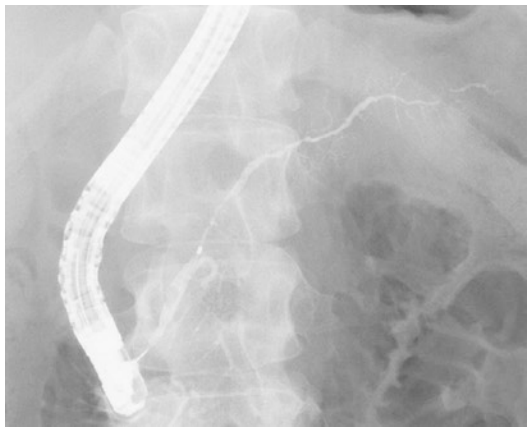

Fig. 15.2 ERCP shows diffuse irregular narrowing of the main pancreatic duct and stenosis of the lower bile duct

gest AIP rather than pancreatic cancer [12]. Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) is widely used to differentiate AIP from pancreatic cancer.

IgG4-SC develops in close association with AIP. In AIP patients, the lower bile duct is frequently stenotic; however, it remains under a debate whether stenosis of the lower bile duct associated with AIP is a primary disease or a direct extension of the inflammatory process from the pancreatic head. In the international consensus diagnostic criteria for AIP, only proximal IgG4-SC is recognized as IgG4-SC [8]. While proximal IgG4-SC frequently occurs in association with AIP, there are a few cases of isolated IgG4-SC that are quite difficult to differentiate from hilar cholangiocarcinoma.

IgG4-Related Sialadenitis and Dacryoadenitis

IgG4-related sialadenitis and dacryoadenitis, known as Mikulicz's disease which consists of bilateral symmetrical swelling of the lacrimal and salivary glands, are now recognized as a form of IgG4-RD.

There are some distinct findings between IgG4-related sialadenitis and Sjögren's syndrome as follows. Submandibular glands are more commonly affected in IgG4-related sialadenitis, while parotid gland enlargement predominates in Sjögren's syndrome. Xerostomia is less severe in IgG4-related sialadenitis than in Sjögren's syndrome, and IgG4-related sialadenitis improves with immunosuppression in contrast to Sjögren's syndrome.

In IgG4-related dacryoadenitis, in addition to (often bilateral) lacrimal glands, other tissues such as extraocular muscles, orbital fat tissues, eyelids, trigeminal nerve branches, and the nasolacrimal duct are sometimes involved. Thus, IgG4-related dacryoadenitis shows various ophthalmological symptoms due to extensive inflammation beyond the lacrimal gland such as eyelid swelling (Fig. 15.3), diplopia, ptosis, visual field disturbance, eye pain, decreased visual acuity, eye movement disturbance, dry eye, corneal ulcer, and epiphora [13].

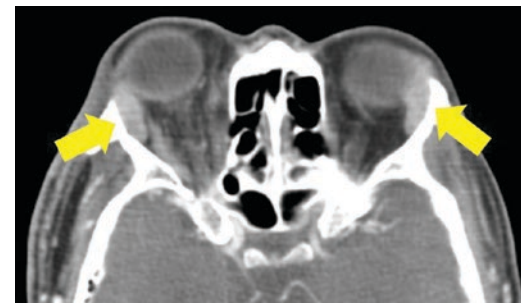

Fig. 15.3 MRI showing bilateral lacrimal gland swelling (arrows)

IgG4-Related Retroperitoneal Fibrosis

IgG4-related retroperitoneal fibrosis is characterized by inflammation and fibrosis of retroperitoneal tissues usually involving the anterior surface of the fourth and fifth lumbar vertebrae, with encasement and obstruction of retroperitoneal structures such as the ureter, aorta, and other abdominal organs. On CT, IgG4-related retroperitoneal fibrosis appears as a periaortic soft tissue density or a mass in the renal hilus with frequent medial deviation and obstruction of ureters, sometimes with hydronephrosis [14].

The management of IgG4-related retroperitoneal fibrosis involves urgent attention to obstructing organs, such as ureters, that require stenting. It should be kept in mind that IgG4-related retroperitoneal fibrosis is sometimes misdiagnosed as retroperitoneal visceral malignancy, resulting in surgery.

IgG4-Related Kidney Disease

A wide range of renal manifestations of IgG4-RD such as TIN, membranous glomerulonephritis and other glomerular lesions, and pyelitis are collectively referred to as IgG4-related kidney disease. More than 80% of patients with IgG4-related kidney disease have other organ involvements.

Contrast-enhanced CT is the most useful imaging system for delineating IgG4-TIN characteristics and distribution of renal lesions. The characteristic imaging findings on enhanced CT in IgG4-related kidney disease are multiple low-density lesions, diffuse kidney enlargement, hypovascular solitary mass in the kidney, and hypertrophic lesion of the renal pelvic wall without irregularity of the renal pelvic surface [9].

Histopathological findings are mandatory for definite diagnosis of IgG4-related kidney disease. However, in several situations such as inaccessible regional lesion distribution (e.g., lesions distributed only in the upper pole of the kidney) that hamper a histological approach, histopathological findings from other organs could support typical renal imaging findings and clinical features of IgG4-related kidney disease to allow diagnosis of IgG4-related kidney disease.

IgG4-Related Lymphadenopathy

Lymphadenopathy is one of the common manifestations in IgG4-RD, with enlarged lymph nodes. As it is usually asymptomatic, it is incidentally pointed out by imaging in many cases.

Generalized lymphadenopathy often clinically and/or histologically resembles lymphoma, Castleman disease, or disseminated malignancy and therefore needs to be distinguished from these diseases [15]. These diseases display fever, weight loss, and elevation of serum CRP, IL-6, and lactate dehydrogenase levels. An abundant infiltration of IgG4-positive plasma cells is a common feature of IgG4-related lymphadenopathy, including Castleman disease-like interfollicular plasmacytosis. Histological diagnosis by lymph node biopsy is required for differentiation from other diseases, especially when lymphadenopathy is not accompanied by other organ manifestations [16].

IgG4-Related Lung Disease

IgG4-related lung disease is reported as inflammatory pseudotumor of the lung with high IgG4 levels. Depending on the radiological findings, IgG4-related lung lesions can be divided into four groups: (1) solid nodular, (2) round-shaped ground-glass opacity, (3) alveolar interstitial, and (4) broncho-vascular [17]. Diagnosis of IgG4-related lung disease is sometimes difficult. Although CT-guided transthoracic core needle biopsy is convenient, it fails to yield a definitive diagnosis in about one-third of all patients. Thoracotomy or video-assisted thoracoscopic surgery (VATS) is therefore recommended to obtain more lung tissue so that a histopathological diagnosis of IgG4-related lung disease can be made.

IgG4-Related Thyroid Disease

IgG4-related thyroid disease is one of the newest identified organ involvement manifestations of IgG4-RD and is yet to be well characterized. To date, Riedel's thyroiditis and the fibrosing variant of Hashimoto's thyroiditis represent IgG4-related thyroid disease types. These disorders are frequently confused with malignancy due to intense sclerosis of the thyroid, which results in a hard texture on palpation, and is compounded by often-associated compressive symptoms [18].

IgG4-Related Cholecystitis

IgG4-related cholecystitis can occur with IgG4-SC. Thickening of the gallbladder wall was detected in 10 of 19 AIP patients on ultrasound and/or CT, and all of the 10 patients had stenosis of the extrahepatic bile duct [19]. There were no symptoms related to the gallbladder. IgG4-related cholecystitis consists of transmural fibrosis with dense infiltration of IgG4-positive plasma cells and lymphocytes [19]. Thickening of the gallbladder wall also improves after steroid therapy.

IgG4-Related Gastrointestinal Disease

While some reports have referred to IgG4-related gastrointestinal diseases, this concept is not well recognized because of insufficient observation. Nevertheless, two types of IgG4-related gastrointestinal disease have been reported. One type is a gastrointestinal lesion that shows marked thickening of the walls of the esophagus and stomach. This lesion consists of dense fibrosis with abundant infiltration of IgG4-positive plasma cells that usually shows submucosal spread. The other type is an IgG4-related pseudotumor that occurs in gastrointestinal lesions, such as the stomach, colon, and major duodenal papilla, and shows polypoid or mass-like lesions. Most solitary IgG4-related gastrointestinal lesions that are not associated with other IgG4-RDs appear to be difficult to diagnose, and it is of the utmost importance to rule out malignancy. However, as these lesions may respond to steroid therapy, IgG4-related gastrointestinal disease should be considered in the differential diagnosis to avoid unnecessary resection [20].

Summary

Diagnosis of IgG4-SC is still challenging, especially differentiation from primary sclerosing cholangitis and hilar cholangiocarcinoma in IgG4-SC involving the hilar bile duct. As it is difficult to obtain adequate biopsy material from the bile duct, association with other IgG4-RDs might aid in diagnosis of IgG4-SC.

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Treatment: Steroids

16

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Introduction

Like autoimmune pancreatitis (AIP), IgG4-related sclerosing cholangitis (IgG4-SC) responds well to steroids, and serum IgG4 falls simultaneously during treatment. Steroid treatment is divided as induction phase, tapering phase, and maintenance phase. Although the starting dose of steroids is not established yet worldwide, it would be reasonable to use the same drug regimen as for AIP, starting at 0.6 mg/kg/day (or 30–60 mg/day) and titrating down the dose as the laboratory results including serum IgG4 improve. A response is expected within 2–4 weeks of steroid treatment. On the other hand, opinion for maintenance treatment is different between Asian and Western countries. The dose is usually tapered to a maintenance dose (2.5–5 mg/day) over a period of 2–3 months, based on changes in clinical manifestations, biochemical blood tests, and imaging findings. Cessation of steroid therapy should be based on the disease activity in each case. The initial response rate to steroid of IgG4-SC was up to 90–97%.

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Induction of Remission

There were no randomized controlled trials of therapy in IgG4-SC. However, based on observational data, steroids are the mainstay of treatment [1–5]. Prior to initiating steroid therapy, it is important to distinguish IgG4-SC from pancreatic or biliary cancer with imaging studies and endoscopic approach [6]. And also, if malignancy is not confirmed by bile duct biopsy in IgG4-SC and bile duct wall thickening that appears normal on a cholangiogram, a steroid trial may be an option [7]. At many institutions, the therapeutic protocol for IgG4-SC follows that for AIP, such as oral prednisolone with the initial dose of 0.5–0.6 mg/kg/day [8]. High-dose steroid therapy (equivalent prednisolone dosing of approximately 30–60 mg/day) results in more rapid and consistent induction of disease remission than conservative management [9]. In Asian countries, the recommended initial oral prednisolone dose for induction of remission is 0.6 mg/kg/day, which is administered for 2–4 weeks. The nationwide survey by the Research Committee of Intractable Pancreatic Disease reported an initial oral prednisolone dose of 30 mg/day (n = 54) or 40 mg/day (n = 32) in 93 AIP patients treated with steroids [9]. The treatment duration necessary to achieve remission in patients treated with an initial prednisolone dose of 30 mg/day averaged 70 days from initial administration, which was not significantly different from those treated

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with an initial prednisolone dose of 40 mg/day (average 91 days). In Western countries, initial prednisolone doses of 50–75 mg/day [10], 40 mg/day [11], and 0.5 mg/kg/day have been reported for steroid treatment [12]. In some patients such as diabetic or elderly patients, a lower dose may be preferred to avoid acute steroid-related complications. However, there are limited data on remission rates using a low dose of steroids (10–20 mg/day) [6, 13]. High-dose steroids are typically administered for 3–4 weeks, followed by an assessment of clinical response. On the other hand, Tomiyama et al. reported that initial steroid pulse therapy is a beneficial alternative to oral steroid therapy for the improvement of bile duct lesions, especially in refractory cases for oral steroids [14].

Because radiological improvement appears within 1 month after the initiation of steroid therapy, morphological and serological evaluation for effectiveness of therapy should be performed after beginning steroid treatment. When the effects of steroids are less than expected, the diagnosis of IgG4-SC needs to be suspected to differentiate bile duct cancer or primary sclerosing cholangitis. Advanced-stage IgG4-SC may sometimes be unresponsive to steroid therapy because cases of AIP and IgG4-SC show a predominantly inflammatory nature at the early stage, followed by relatively less inflammation but marked fibrous scarring later.

Tapering of Steroid

After 2–4 weeks at the initial steroid dose, the dose is gradually tapered by 5 mg every 1–2 weeks based on changes in clinical manifestations, biochemical blood tests including liver enzymes or IgG4 level, and imaging findings. The dose is tapered and reached to a maintenance dose over a period of 3–6 months [6, 8]. At the Mayo Clinic, an initial prednisolone dose of 40 mg/day was administered for 4 weeks, followed by tapering of 5 mg/week (total of 11 weeks of treatment) [11]. As reported by Park et al. in South Korea, the induction dosage of prednisolone was initially administered at 0.5 mg/kg/day for 1–2 months and was gradually reduced by 5–10 mg/month to a maintenance dose, and maintenance therapy was discontinued completely after an average period of 6 months [15].

Maintenance Therapy

Although there is no clear high-level evidence and consensus regarding maintenance steroid therapy, steroid treatment in Japan and South Korea is often discontinued after a certain period of maintenance therapy [1–3, 8]. A multicenter study in Japan reported that 377 (82%) of 459 steroid-treated patients received maintenance therapy with steroids [6]. A maintenance dose of 5 mg/day of oral prednisolone was most common (63%), followed by 2.5 mg/day (21%), 10 mg/day (7%), and 7.5 mg/day (3%) [8]. The reasons are as follows: in the international study, the majority of relapse episodes have occurred in steroid-treated patients following steroid discontinuation (67%), as compared to during steroid taper (15%) or while on maintenance steroid therapy (18%) [16]. And also, Kamisawa et al. showed a decreased rate of disease relapse with maintenance corticosteroid therapy compared with no maintenance therapy (23% vs. 34%; $P = 0.045$) [6]. In recent large-scaled study, Tanaka et al. reported the steroid treatment results of 458 patients who were diagnosed with IgG4-SC. Maintenance therapy was performed in 63% ($n = 309$) of patients with IgG4-SC. The oral steroid doses used for maintenance therapy were ≤5 mg in 220 patients [17].

In contrast, steroid therapy protocol without maintenance therapy is common in Europe and North America [11, 16, 18]. Those countries favored to minimize cumulative corticosteroid exposure; corticosteroid therapy is completely withdrawn after successful induction of remission [19]. The most commonly used protocol consists of high-dose corticosteroids for 4 weeks followed by a taper of 5 mg each week until discontinued [11]. In the recent European study, a total of 98 patients received oral steroids without maintenance therapy; initial steroid dose was 0.5 mg/kg for 2–4 weeks of induction. Steroid therapy was stopped after median duration of 5.5 (range 1–73) months [13].

However, as IgG4-SC patients with long-term steroid therapy are at high risk of developing steroid-related complications such as osteoporosis, increased susceptibility to infection, and diabetes mellitus, discontinuation of steroid treatment should be considered. Cessation of maintenance therapy should be planned within 3 years in cases with radiological and serological improvement. When steroid treatment is discontinued, patients should be followed up for relapse of IgG4-SC [8].

Conclusions

As with other disease manifestations of IgG4-RD, steroid therapy is the treatment of choice in IgG4-SC and generally leads to the rapid and consistent induction of disease remission. Long-term survival is excellent in IgG4-SC after adequate therapy, and surgery for biliary strictures is not needed in most cases. To date, there is no international consensus on an appropriate steroid regimen, duration of treatment, or the maintenance therapy because of a lack of randomized clinical trials. Nevertheless, several studies seem to show a benefit on relapse rates of long-term treatment with low-dose corticosteroids (2.5–5 mg/day) compared with no maintenance treatment [11, 19]. Caution is necessary when oral steroids are used in patients with IgG4-SC.

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Treatment: Immunomodulatory Drugs

17

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Introduction

The Japanese clinical diagnostic criteria for IgG4-related sclerosing cholangitis (SC) established in 2012 are useful in the diagnosis of IgG4-related cholangiopathy [1]. IgG4-related SC, a distinctive type of cholangitis of unknown etiology, is characterized by increased serum levels of IgG4 and massive infiltration of IgG4-positive plasma cells with extensive fibrosis in the wall of the bile duct. Its cholangiographic features are similar to those of primary sclerosing cholangitis (PSC), pancreatic cancer, and cholangiocarcinoma. However, it has been reported that about approximately 60–85% of patients with type 1 autoimmune pancreatitis (AIP) have associated with IgG4-SC [1–5]. The steroid responses and the prognoses of IgG4-SC differ from those of patients with PSC, which suggests different pathologies. IgG4-SC responds well to steroid therapy, and the recommended first-line treatment for IgG4-SC is corticosteroid therapy. Unfortunately, despite the high initial remission rates, 15–60% of patients will develop disease relapse either after cessation of steroid therapy or during the weaning of the steroid dose [6–9]. In Japan, to prevent relapses in type 1 AIP (including IgG4-SC), many patients are advised to continue daily low-dose prednisolone (2.5–10 mg) for months to years following induction of remission. However, this maintenance of steroid therapy has its advantages and disadvantages. Recently, the outcome of a Japanese randomized controlled study regarding maintenance steroid therapy was reported [10]. In general, IgG4-SC is treated with steroids, immunomodulatory drugs, or rituximab. Herein, we discuss the treatment of IgG4-SC, focusing on immunomodulatory agents.

Immunomodulatory Agents

In inflammatory gastrointestinal disorders, such as autoimmune hepatitis (AIH) and inflammatory bowel disease (IBD), many gastroenterologists have an experience of prescribing immunomodulatory drugs, such as azathioprine (AZA), 6-mercaptopurine (6-MP), and mycophenolate mofetil (MMF) (not use for AIH or IBD in Japan). These drugs have also been used to treat patients with IgG4-SC and type 1 AIP.

AZA is a prodrug that is converted to 6-MP in the body. Both AZA and 6-MP are metabolized to cytotoxic thioguanine nucleotides, which act as purine analogs. These analogs can inhibit purine synthesis (by inhibiting glutamine-phosphoribosyl pyrophosphate amidotransferase), thereby preventing cell proliferation, especially leuko-

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cytes and lymphocytes. Therefore, both cell-mediated and antibody-mediated immunoreactions are suppressed. Although there are other common adverse effects, such as nausea and vomiting, the most severe side effect is known as bone marrow suppression, and, for this reason, it should not be given in conjunction with purine analogs such as allopurinol. The enzyme thiopurine S-methyltransferase (TPMT) is known to deactivate 6-MP. Genetic polymorphisms of TPMT, which reduce or negative its activity, can lead to excessive drug toxicity. Thus, assays of serum TPMT activity may be useful to prevent this dangerous complication.

MMF is a prodrug of mycophenolic acid (MPA), which impedes purine synthesis by inhibiting inosine monophosphate dehydrogenase (IMPDH). MMF is the morpholinoethyl ester of MPA, esterified to improve its bioavailability, and converted back to MPA in the liver. MPA is a potent, selective, uncompetitive, and reversible inhibitor of IMPDH, and therefore inhibits the de novo pathway of guanosine nucleotide synthesis, without incorporation into DNA. Because T and B cells are critically dependent on de novo synthesis of purine synthesis for their proliferation, whereas other cell types can utilize salvage pathways, MPA has potent cytostatic activities on lymphocytes. MPA inhibits proliferative responses of T and B cells to both mitogenic and allospecific stimulation. The addition of guanosine or deoxyguanosine reverses these cytostatic activities of MPA on lymphocytes.

MPA also suppresses antibody production by B cells. MPA prevents the glycosylation of lymphocytic and monocytic glycoproteins that are involved in cell-cell adhesion to endothelial cells, which may inhibit recruitment of leukocytes to the inflammatory site. MMF does not inhibit early events in the activation of mononuclear cells in peripheral blood, such as the production of interleukin-1 (IL-1) and interleukin-2 (IL-2), but it did block the coupling of these events to DNA synthesis and proliferation.

In general, AZA is more myelotoxic and hepatotoxic than MMF is, but MMF causes diarrhea in 30% of patients and can cause tissue-invasive cytomegalovirus (CMV) infections. Using either drug in the long term also appears to increase slightly the risk of developing lymphoma [11, 12].

Efficacy of Immunomodulatory Drugs in IgG4-SC

In Japan, it is recommended that maintenance steroid therapy should be administered for 3 years to type 1 AIP patients in order to reduce the incidence of relapse [13]. In western countries, steroid treatment is often limited to a short-term therapy due to ongoing concerns about the risks of adverse events, such as diabetes mellitus, osteoporosis, cataract, peptic ulcer, and infection [14]. While concomitant steroid therapy is necessary to induce remission when these immunomodulatory drugs are used, their primary benefit is the avoidance of long-term steroid exposure in a disease population that generally consists of older patients.

There have been some case reports from Asian countries that support the usefulness of immunomodulatory drugs for IgG4-SC [15, 16]. Generally, it is believed that immunomodulatory drugs, such as AZA, lack effectiveness as single agents to induce remission. In western countries, immunomodulatory drugs have recently been introduced to treat type 1 AIP and IgG4-SC patients who had relapsed or who were resistant to steroid therapy. Regarding relapse cases treated with immunomodulatory drugs, both advantages and disadvantages have been reported. We will present four reports advocating the usefulness of AZA treatment, followed by a single report of the ineffectiveness of using AZA and MMF.

First, from Pittsburgh Medical Center, a retrospective case review described the use of steroid therapy in 19 patients and methotrexate in 1 patient, out of a total of 26 patients. Nine of 26 patients showed IgG4-SC. Among the 15 of 19 patients with a complete response, 9 had a recurrence within 8–12 weeks of steroid withdrawal, with 4 patients presenting as recurrent biliary strictures. Recurrences were treated with corticosteroids during the acute flare-up, and AZA was added for long-term immunosuppression.

All 9 patients responded and were maintained on long-term AZA. Among the 4 patients with incomplete response to steroids, three eventually responded to a combination of prednisone and AZA, followed by AZA alone. The remaining patient with an incomplete response to steroids was also started on AZA. Therefore, this article reported the usefulness of AZA for steroid-resistance patients [17].

Second, a group from the United Kingdom described the use of steroid therapy in 28 AIP patients. The investigators found that 13 patients with IgG4-SC relapsed (5 patients relapsed during maintenance steroid therapy and 8 patients relapsed after steroid discontinuation). The prednisolone dose was increased (to 20–30 mg/day) in all 13 of the patients who relapsed, and 10 of these patients also received AZA (1–2 mg/kg/day). Remission was subsequently achieved in 12 patients. However, after second remission, 1 of 7 patients who underwent AZA monotherapy and 2 of 3 patients who underwent maintenance therapy with AZA and concomitant steroid relapsed again. The investigators concluded that AZA was effective in patients with posttreatment relapse or in those who could not be weaned from steroids [7].

Third, an international retrospective study induced with a total of 1064 subjects were identified, 978 with type 1 AIP and 86 with type 2 AIP. Of the 978 subjects with type 1 AIP, a total of 302 (31%) experienced at least one disease relapse during the study period, compared to 8 (9%, $p < 0.001$) with type 2 AIP. This report showed successful induction in 56 of 68 (85%) relapsing patients by the addition of AZA and successful remission with follow-up in 86% of those who received immunomodulatory drugs. Of course, steroids were the most commonly used treatment for managing disease relapse in type 1 AIP, and remission induction was successful in 201/210 (95%) of subjects. This report also recognized the usefulness of the addition of AZA for relapsed cases [18].

Fourth, an Italian group recently reported the efficacy of AZA as a maintenance therapy to prevent disease relapse in AIP. Twenty-three patients in the group treated with AZA (2–2.5 mg/kg/day) and 97 in untreated group without maintenance therapy were compared. In the group treated with AZA versus the untreated group, the patients were significantly older ($p = 0.043$), type 1 AIP was more frequently diagnosed (87 vs. 51%, $p = 0.006$), serum IgG4 was higher (758 ± 625 vs. 311 ± 409 mg/dl, $p < 0.001$), other organ involvement (included IgG4-SC, (OOI)) was more frequently observed (83 vs. 48%, $p = 0.002$), and there was a higher frequency of relapse before AZA treatment (78 vs. 14%, $p < 0.001$). Three patients in the AZA-treated group discontinued the drug because of adverse events. Therefore, 20 patients were evaluated for outcome. Six out of 20 patients (30%) relapsed after 24 ± 15 months (5 in the pancreas and 1 on biliary tract); they were treated again with steroids, and then they continued AZA. Two out of these 6 patients (33%) had a second relapse, after, respectively, 11 months (in the pancreas and kidney) and 22 months (in the kidney). The study authors concluded that AZA is an effective and safe treatment to prevent AIP relapses [19].

The last report presented cases of treatment with immunomodulatory drugs (AZA and MMF). A study from the Mayo Clinic on the administration of AZA (2–2.5 mg/kg/day) or MMF (1500 mg/day) in 7 patients with type 1 AIP and IgG4-SC, who had relapsed once or twice, or with IgG4-SC without type 1 AIP, reported that no relapse was observed (median observation period 6 months, range 2–19 months). In 2 of the 7 patients, low doses of AZA (50 mg/day) and MMF (1000 mg/day) were administered initially, but both patients relapsed. They concluded that relapse-free survival is similar in patients treated with steroids plus immunomodulatory drugs compared to those treated with steroids alone, and nearly half of the patients on immunomodulatory drugs will relapse during treatment [20].

Immunomodulatory drugs, such as AZA, may have a modest benefit in the maintenance of remission in patients with IgG4-SC. However, many of the treated patients developed relapse during treatment, are unable to be weaned from steroids, or must discontinue treatment due to side effects. Therefore, additional treatment options are needed. It is possible that alternative

immunomodulatory drugs will be more effective than AZA. Further examination of these immunomodulatory drugs is necessary.

Summary

The most studied immunomodulatory drugs are AZA, 6-MP, and MMF. They are used as steroid-sparing agents. Unlike these drugs, they are not effective as single agents to induce remission after relapses. Immunomodulatory drugs require overlap with steroids for 6–8 weeks, and the disease must be in remission to subsequently withdraw the steroids. However, while the use of immunomodulatory drugs as second-line therapies for refractory cases is expected to become increasingly prevalent, these drugs are associated with serious side effects and should be considered with caution. Alternative therapy may be needed.

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Treatment: Rituximab

18

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Introduction

A steroid-responsive cholangiopathy associated with thyroiditis, sialoadenitis, and hypergammaglobulinemia was first described in 1963 [1] and again in 1979 [2], and the discovery by Japanese investigators of serum IgG4 as a biomarker of autoimmune pancreatitis [3] has led to increased recognition of both pancreatic and biliary IgG4-related disease (IgG4-RD). Hepatobiliary involvement by IgG4-RD is currently termed IgG4-associated sclerosing cholangitis (IgG4-SC) and in the past has been called IgG4-associated cholangitis (IAC) or IgG4-related cholangitis (IRC). IgG4-SC may involve the intrahepatic and/or extrahepatic bile ducts and may mimic the biliary strictures of chronic pancreatitis, hilar cholangiocarcinoma, or intrahepatic sclerosing cholangitis. Diagnosis of IgG4-SC may be particularly difficult if the biliary tree is the sole anatomical area affected. The classification and diagnostic approach to IgG4-SC are discussed in other chapters.

Although most cases of IgG4-SC are steroid responsive, some patients are unable to discontinue steroid therapy or relapse after steroids are withdrawn, and occasional patients do not respond adequately to steroid treatment [4]. This has led several investigators worldwide to explore alternative treatment strategies. In this chapter, we will focus on the role of rituximab (RTX) in the treatment of IgG4-SC.

Definition of Treatment Response

Successful treatment of IgG4-SC may not result in radiologic normalization of the biliary tree, and residual ductal strictures may be due to fibrosis that persists after the inflammatory process has resolved. Definition of treatment outcomes is important to guide judicious treatment decisions and for comparing effectiveness of different treatment modalities. We use the following terms and definitions for treatment response in IgG4-SC:

(a) Complete remission: Resolution of symptoms and imaging or laboratory findings of active IgG4-RD (clinical, radiographic, and biochemical), without an ongoing need for medical therapy (Fig. 18.1)
(b) Partial remission: Improvement without resolution of inflammatory changes, without an ongoing need for medical therapy
(c) Incomplete remission: Improvement without resolution of inflammatory changes and with ongoing need for medical therapy to maintain response

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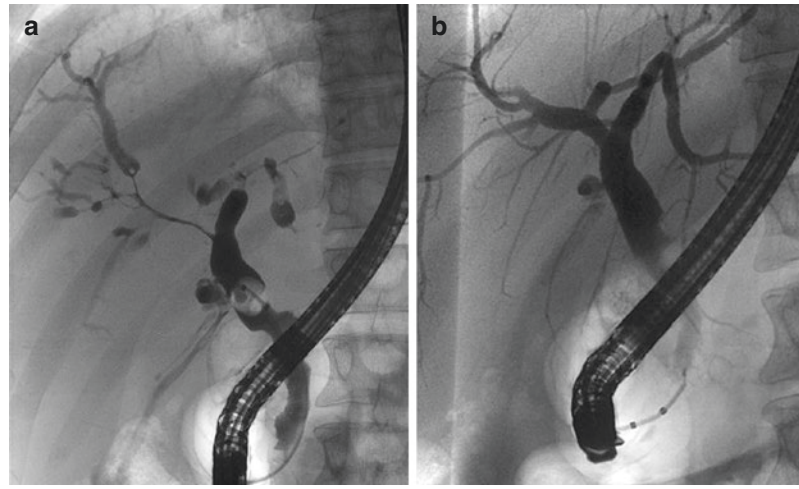

Fig. 18.1 Endoscopic cholangiogram before (**a**) and after (**b**) treatment for IgG4-SC in a patient who achieved complete remission

(d) Relapse: Development of symptoms, radiologic findings, and/or biochemical abnormalities consistent with a new or worsening inflammatory process after previous successful medical therapy, requiring retreatment
(e) Recrudescence: Development of symptoms, radiologic findings, and/or biochemical abnormalities consistent with a new or worsening inflammatory process during steroid taper and requiring an increase in the dose of steroids or additional treatments

Rituximab (RTX)

RTX is a chimeric mouse-human monoclonal antibody that binds specifically to the CD20 antigen, a transmembrane receptor located on the cell surface of pre-B and mature B lymphocytes, and induces apoptosis. RTX was initially approved by the US Food and Drug Administration in 1997 to treat resistant B-cell non-Hodgkin lymphomas. Subsequently it was approved for use in rheumatoid arthritis and has been used off-label in other autoimmune and inflammatory conditions including systemic lupus erythematosus, idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, and pemphigus vulgaris. RTX was also shown to be effective in treating orbital pseudolymphoma [5], a manifestation of IgG4-RD, and pemphigus vulgaris, which is characterized by the presence of IgG4 antibodies. Primarily because of its efficacy in treatment of hematologic malignancies, RTX is on the World Health Organization's List of Essential Medicines.

The physiological effect of RTX can be monitored by flow cytometry of peripheral blood. After RTX administration, B lymphocytes (CD19- or CD20-positive cells) disappear from the peripheral circulation. Flow cytometry can be performed at intervals (for instance, 6 months after induction RTX therapy and then every 3 months thereafter) to guide decisions about maintenance infusions, if desired. Human antichimeric antibodies (HACA) directed against the murine fragments of RTX have been described and may be associated with lack of therapeutic response [6].

Rituximab is administered as a slow intravenous infusion. The optimum RTX regimen for treating IgG4-SC is unknown, and treatment regimens continue to evolve. Initially we used a lymphoma regimen that included induction with four weekly infusions of 375 mg/m^2 followed by a maintenance infusion of 375 mg/m^2 every 3 months for up to 2 years. Currently we typically prescribe two induction doses of 1000 mg spaced 2 weeks apart, with or without subsequent maintenance infusions of 1000 mg every 6 months or when B cells return in the peripheral blood. However, as the overall experience continues to grow, future studies are expected to further refine these regimens to optimize patient outcomes.

RTX in IgG4-SC

The overall experience with RTX for IgG4-SC is limited, and there are no randomized or placebo-controlled data available. A case of RTX therapy for IgG4-SC refractory to steroid therapy was reported in 2008 [4]. A case series of 12 patients with autoimmune pancreatitis, 7 with concomitant IgG4-SC, who were treated with RTX induction followed by maintenance dosing was reported in 2013 [7]. Of the seven patients with IgG4-SC, five had a complete remission, one had an incomplete remission (requiring low-dose steroid therapy), and one had a partial remission followed by worsening cholestasis and was found to have cholangiocarcinoma. The use of RTX was also described in a prospective open-label clinical trial of 30 patients with IgG4-RD, including 10 with IgG4-SC [8]. A treatment response was seen in 97% of patients in the trial, and all patients with IgG4-SC achieved a complete remission. In this cohort of patients, two induction doses of RTX were administered without maintenance therapy, and at 6 months postinduction, less than 80% of patients were steroid-free. In another retrospective study of 60 patients receiving RTX induction therapy for IgG4-RD, including five with biliary or hepatic IgG4-RD, almost half of patients had relapsed within 1 year [9]. We recently reviewed our institutional experience comparing RTX induction and maintenance therapy (n = 29) to induction therapy alone (n = 14) in pancreaticobiliary IgG4-RD, including 35 patients with IgG4-SC [10]. Overall, 86% patients in this study, the majority of whom had relapsing or recrudescent disease, were in steroid-free remission 6 months after initiating RTX. Relapses were more common in those treated with induction alone compared to those also receiving maintenance RTX (3-year event rate 45% vs. 11%). Maintenance therapy effectively prolonged remission, but the relapse rate after treatment discontinuation was not significantly different between the two groups. Although RTX was fairly well tolerated in this cohort, maintenance therapy was associated with an increased risk of bacterial infections, which occurred in 5 of 29 patients during maintenance therapy.

Adverse Effects of RTX

The adverse effects of RTX have been investigated in large series of patients receiving the drug for hematologic malignancies or other inflammatory diseases. In contrast to corticosteroids, the majority of patients receiving RTX experience no adverse effects of the drug. Certain adverse effects, such as tumor lysis syndrome and bowel perforation related to tumor lysis, are seen only in patients with malignancies. The main adverse effects of RTX in treatment of benign disorders are:

(a) Infusion reactions. Mild infusion reactions are commonly Grade 1 or 2 reactions (characterized by a rash, pruritus, flushing, urticarial, nausea/vomiting, throat or chest tightness, or asymptomatic bronchospasm) and are usually treated by stopping the infusion, administering intravenous antihistamines (H1 and H2 blockers), allowing findings to resolve, and then resuming the infusion at a slower rate [11]. Patients with Grade 3 or 4 infusion reactions (including symptomatic bronchospasm, dyspnea, hypoxia, wheezing, anaphylaxis, or hypotension) may have recurrent symptoms during same-day rechallenge and may benefit from further evaluation prior to rechallenge [11]. Severe, sometimes fatal, infusion reactions, including anaphylaxis, shock, acute respiratory distress syndrome, and myocardial infarction, have been reported in 0.04–0.07% of patients receiving rituximab. Severe mucocutaneous reactions, including Stevens-Johnson syndrome, have also been reported. Premedications (often including methylprednisolone 100 mg IV, oral acetaminophen, and diphenhydramine) are given prior to infusions to decrease the incidence of infusion reactions.

Cytokine release syndrome may occur with rituximab infusions. This syndrome mimics sepsis and is characterized by fever, rigors, and hypotension. This adverse effect is uncommon, especially when premedications are administered.

(b) Infectious complications. Rituximab can cause reactivation of hepatitis B virus (HBV) infection, sometimes leading to fulminant hepatitis. Patients who are hepatitis B surface antigen (HBsAg) positive are at high risk. Patients who are HBsAg negative but have HBV core antibodies (HBcAb+) are also at risk of reactivation, even if HBV DNA is undetectable in their blood [12], and in such patients suppressive therapy with a nucleotide or nucleoside analog should be considered for the duration of rituximab therapy (i.e., until B cells return to the peripheral circulation). In addition, reactivation of tuberculosis (TB) may occur on rituximab therapy, and guidelines recommend screening patients for TB exposure (for instance, with a QuantiFERON test) prior to prescribing RTX.

Serious bacterial infections may occur at an increased rate in patients receiving RTX. In a registry analysis of patients with rheumatoid arthritis receiving RTX, predisposing factors for bacterial infections included age, comorbidities, and low initial serum immunoglobulin G levels [13]. Patients with baseline serum IgG levels of <6 g/L may be at a fivefold increased risk, and this should be taken into account when considering RTX therapy.

(c) Progressive multifocal leukoencephalopathy (PML). PML is a frequently fatal demyelinating infection of the central nervous system caused by reactivation of JC polyomavirus infection. Neurologic presentation is highly variable depending on the regions of the brain that are affected. PML has been associated with RTX therapy, however the absolute risk is small (estimated at 1 in 20,000 rheumatoid arthritis patients receiving RTX) [14]. Pretreatment screening for JC virus infection is not recommended as over half of the adult American population has serologic evidence of prior infection.

(d) Cytopenias and hypogammaglobulinemia. These may develop following RTX induction therapy, and low immunoglobulin levels may be associated with increased rates of bacterial infections. Neutropenia is uncommon, may occur up to 1 year after RTX therapy, and is probably not an absolute contraindication to repeat RTX treatment.

Predictors of Relapse After RTX Induction Therapy

In our experience, elevated pre-RTX alkaline phosphatase levels are associated with a higher risk of relapse. Compared to patients with AIP, those with IgG4-SC were three times more likely to relapse if their alkaline phosphatase normalized with induction RTX therapy and six times more likely to relapse if their alkaline phosphatase did not normalize with induction therapy [10]. These findings highlight the high risk of disease recurrence in patients with IgG4-SC, many of whom will need repeat courses of treatment or maintenance treatment to prevent progressive liver disease.

In studies of various manifestations of IgG4-RD treated with RTX, elevations in pretreatment serum IgG4, immunoglobulin E (IgE), and blood eosinophil concentrations independently predicted future relapses in IgG4-RD. [9] Data from our center suggest that younger age and a higher IgG4-RI (IgG4-Responder Index) [15] score after induction RTX therapy are also associated with a higher likelihood of relapse in pancreaticobiliary IgG4-RD. [10] Future studies aimed at identifying predictors of relapse after RTX induction therapy are needed to identify the optimum duration of RTX treatment and guide accurate selection of patients who would benefit the most from maintenance RTX therapy.

Which Patients Should Be Considered for RTX Therapy?

While steroids remain the mainstay of initial treatment for IgG4-RD, relapse is likely in those with proximal biliary strictures. We have seen relapsing IgG4-SC rapidly lead to decompensated biliary cirrhosis and death. Therefore we monitor patients for relapse after successful steroid therapy,

including periodic measurement of serum liver tests to detect recurrent cholestasis, and promptly advise additional therapy when relapse occurs. In our experience, traditional oral immunomodulators are not effective for prevention of relapse [7], and we no longer use these drugs routinely in our practice, favoring RTX therapy in patients with relapsing disease. In addition, we may consider RTX as an initial therapeutic option in patients with a history of or risk factors for steroid intolerance and in those who are not responding to steroid therapy or unable to successfully taper steroids. An algorithm for treatment of IgG4-SC incorporating RTX therapy is shown in Fig. 18.2. Prior to initiating RTX therapy, we measure serum IgG levels and screen patients for tuberculosis, HIV, hepatitis B, and hepatitis C.

Future Directions

Although available data support a role of RTX in managing patients with IgG4-SC, several key questions remain unanswered at this time. Most importantly, the optimum duration of RTX therapy needs to be better defined. It is also equally important to study long-term adverse effects of RTX, to explore alternative treatments that might more reliably induce a sustained clinical remission, and identify biomarkers that predict relapse and can be used to individualize therapy. Randomized clinical trials are needed to study the role of RTX as first-line therapy in IgG4-SC with the goal of sustained remission, improved patient outcomes, and cost-effectiveness.

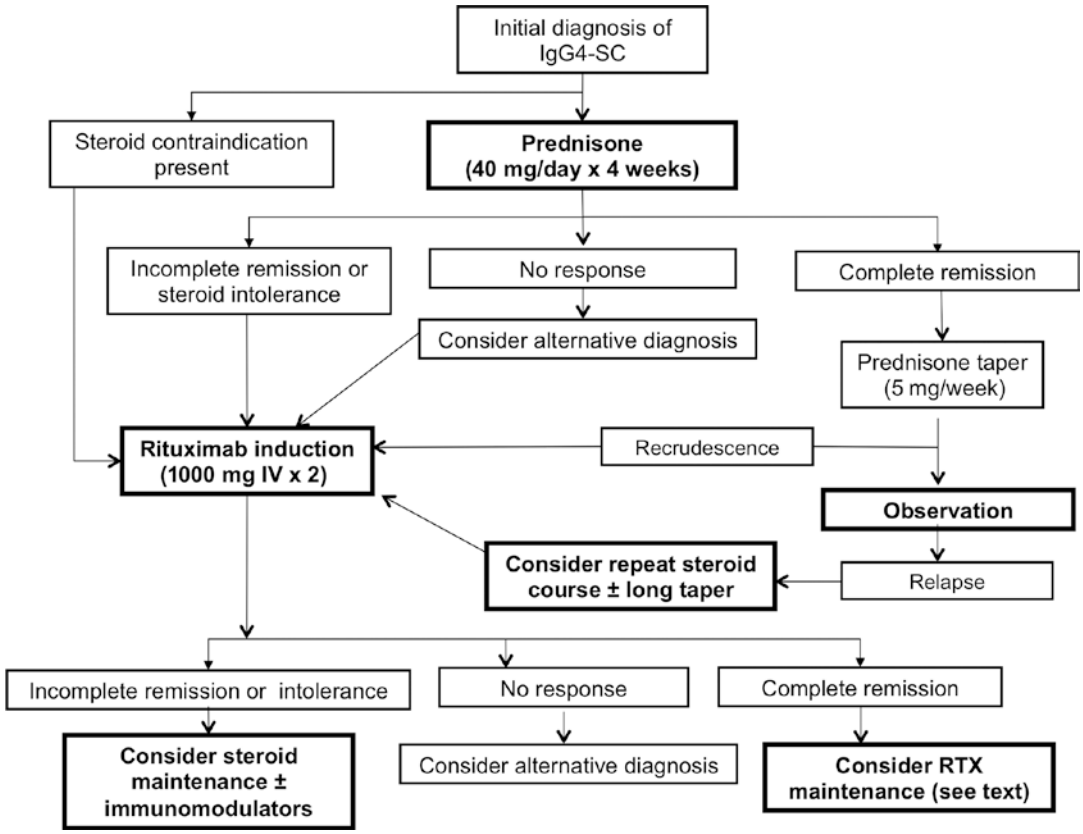

Fig. 18.2 Treatment algorithm for IgG4-SC incorporating rituximab therapy

Conclusion

The management of patients with IgG4-SC poses several challenges. Diagnosis may be difficult, response to steroid therapy may be suboptimal, and relapse is common. For patients with relapsing disease or contraindications to steroid use, RTX is the only agent currently available that will reliably induce remission. Maintenance therapy with RTX appears to effectively prolong remission and may be warranted, particularly in patients with persistent or recurrent serum alkaline phosphatase elevations. Patients receiving RTX should be screened and monitored for infections and should receive infusions in a therapeutic infusion center where infusion reactions can be properly assessed and treated.

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Prognosis

19

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Introduction

IgG4-related sclerosing cholangitis (IgG4-SC) is a biliary manifestation of a systemic condition known as IgG4-related disease (IgG4-RD). IgG4-RD may involve various organs with type 1 autoimmune pancreatitis (AIP) being the leading manifestation. Older men are more affected by IgG4-SC than women (ratio of 4:1), and the most common clinical manifestation is obstructive jaundice. The pathogenic mechanism of IgG4-SC remains unclear [1]. Steroid therapy can lead to clinical and radiological improvement when provided in the inflammatory phase of this disease. However, long-term outcome data in patients with IgG4-SC are lacking. In this chapter, we focus on the prognosis of IgG4-SC, including the natural course, treatment response, risk of malignancy, and long-term outcome, based on current evidence.

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Natural Course

The natural history of IgG4-SC has not been well defined. Nakazawa et al. reported a classification of cholangiographic changes in IgG4-SC as follows: stenosis is located only in the lower part of the common bile duct in type 1; stenosis is diffusely distributed in the intra- and extrahepatic bile ducts in type 2; stenosis is detected in hilar hepatic lesions and the lower part of the common bile duct in type 3; and strictures of the bile duct are detected only in hilar hepatic lesions in type 4 [2]. Substantial spontaneous improvement is sometimes observed in type 1 IgG4-SC, with improvement of strictures probably correlating with reduced pancreatic inflammation around the distal common bile duct. However, in IgG4-SC types 2–4, an improvement without treatment is unusual [3]. Most AIP cases that spontaneously improve do not have bile duct stenosis. Kamisawa et al. noted that, among 21 patients with AIP, spontaneous improvement was detected in two (10%) patients without jaundice [4]. Kubota et al. compared clinicopathological parameters in 8 patients with AIP and remission in the absence of steroid therapy and in 12 patients with remission after steroid therapy [5]. They found an association between spontaneous remission and the absence of obstructive jaundice. Based on these

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observations, spontaneous remission of bile duct stenosis in IgG4-SC appears to be rare, except for some type 1 cases.

Treatment Response and Relapse

The aims of treatment in IgG4-RD are to alleviate symptoms and to prevent disease-related complications and irreversible fibrosis. An international consensus of experts on disease management concluded that urgent treatment is appropriate in biliary disease, even when asymptomatic, to prevent infectious cholangitis and permanent fibrosis that might complicate untreated disease [6]. Despite an absence of randomized, placebo-controlled trials, the mainstay of treatment for IgG4-RD is systemic corticosteroids, extrapolated from findings in AIP. Kamisawa et al. reported that use of steroid-induced remission was quicker and more consistent and had a lower relapse rate compared with the conservative approach in 563 patients with AIP, 314 (55.8%) of whom had coexisting IgG4-SC (Table 19.1) [7].

Comparison among studies can be difficult because of heterogeneous patient groups, use of different diagnostic criteria, and definitions of response. Despite these limitations, most patients with IgG4-SC respond to steroid therapy. Ghazale et al. reported an illustrative series including 53 patients with IgG4-SC, 30 of whom were treated initially with prednisone (40 mg/day for 4 weeks followed by tapering of 5 mg per week for a total of 11 weeks) (Table 19.1) [8]. An initial response to glucocorticoids was observed in 29 (97%) of these patients, but only 18 (60%) had resolution of strictures and normalization of liver biochemical tests. Sandanayake et al. performed a prospective study that evaluated 28 patients with AIP, 23 of whom had coexisting IgG4-SC (Table 19.1) [9]. All of the patients responded within 6 weeks to glucocorticoid therapy (prednisolone 30 mg/day followed by tapering of 5 mg per every 2 weeks). A total of 23 (82%) patients achieved remission after a median of 5 months of treatment (range 1.5–17 months), whereas 5 (18%) patients could not be weaned because of a disease flare.

Patients with IgG4-SC are at high risk of relapse, the majority of which occurs within 6 months of discontinuing or tapering steroid treatment. Relapse rates have been reported in approximately 30–50% of patients after cortico-

Table 19.1 Treatment response and relapse rate of patients with IgG4-SC

Reference	IgG4-SC/ IgG4-RD[a] (%)	Treatment[a]		Response to treatment[a] (%)	Relapse[a] (%)	Follow-up[b] (range)
Kamisawa et al. [7]	314/563 (56)	Steroid therapy	459	451/459 (98)	110/451 (24)	N.A.
		Surgical resection or observation	104	77/104 (74)	32/77 (42)	
Ghazale et al. [8]	53/53 (100)	Steroid therapy	30	29/30 (97)	16/30 (53)	29.5
		Surgical resection	18	18/18 (100)	8/18 (44)	58
		Conservative	5	N.A.	0 (0)	35
Sandanayake et al. [9]	23/28 (82)	Steroid therapy	28	28/28 (100)	8/23 (35)	29 (6–53)
Huggett et al. [10]	68/115 (59)	Steroid therapy	98	95/97 (97)	58/115 (50)	32.5 (0.8–107)
		Surgical resection or observation	17	N.A.		
Hart et al. [11]	458/724 (63)	Steroid therapy	684	681 (99)	245/681 (36)	N.A.
		Surgical resection	150	147 (98)	46/139 (33)	
		Conservative	67	37 (55)	11/57 (19)	

IgG4-SC IgG4-related sclerosing cholangitis, *IgG4-RD* IgG4-related disease, *N.A.* not available
[a]The number of patients is shown
[b]Median months of follow-up are shown

steroid therapy (Table 19.1). Known risk factors for relapse include increased IgG4 levels and the presence of proximal bile duct strictures [7–11]. Relapsed disease develops either at the same site as the original disease or in a different portion of the biliary tree. New lesions may also appear in other organs. Additional high-dose steroids remain highly successful for reinduction of remission in patients with relapse. Other approaches include immunomodulators, such as azathioprine, 6-mercaptopurine, and mycophenolate mofetil. However, no reliable data are available in terms of how effective these drugs are in reinduction of remission in patients with relapsed IgG4-SC [11].

Rituximab, a monoclonal CD20 antibody leading to B-cell depletion, has been increasingly recognized as a promising treatment for IgG4-RD [12, 13]. The first reported patient with IgG4-RD who was administered rituximab had relapsed IgG4-SC and was refractory to steroids and 6-mercaptopurine [13]. This patient was treated with rituximab, and remission was successfully achieved. Based on the findings of subsequent studies, including a recent phase I/II study, rituximab appears to be effective for inducing and maintaining remission [11, 13, 14]. Therefore, rituximab may be worth considering for patients with previous intolerance to high-dose steroids and those at a high risk of relapse [12, 13]. Therefore, as is the case with IgG4-RD in other organs, the initial response to glucocorticoids is favorable, but treatment for steroid-refractory cases of IgG4-SC needs further study.

Risk of Malignancy

Some studies have suggested that the presence of IgG4-RD is associated with an increased risk of malignancy, which may involve a variety of organs and tissues. This risk may be particularly increased in the year after diagnosis of IgG4-RD. However, other studies have not found such a risk, and this issue remains controversial.

Huggett et al. reported the risk of type 1 AIP and IgG4-SC in patients in a UK cohort [10]. A total of 115 patients, 68 (59%) of whom had IgG4-SC, were included, with a median follow-up from diagnosis of 32.5 months (range: 0.8–107 months). At least 12-month follow-up data were available for 88 patients (77% of the cohort). Among 115 patients, 13 (11%) were diagnosed with a malignancy within 3 years before the diagnosis of IgG4-RD, concurrently, or during follow-up, including three hepatopancreaticobiliary cancers. The risk of any cancer at diagnosis or during follow-up compared with matched national statistics was increased (odds ratio, 2.25; 95% confidence interval [CI] 1.12–3.94). We also reported that patients with type 1 AIP were at high risk of having various cancers [15]. In a series of 108 Japanese patients with AIP, 57 (52.8%) of whom had coexisting IgG4-SC, 18 cancers were found in 15 (13.9%) patients; the median follow-up was 3.3 years. The standardized incidence ratio (SIR) of cancer was 2.7 (95% CI 1.4–3.9), which was stratified into the first year (6.1, 95% CI 2.3–9.9) and subsequent years (1.5, 95% CI 0.3–2.8) after diagnosis of AIP. The relative risk of cancer among patients with AIP at the time of diagnosis of AIP was 4.9 (95% CI 1.7–14.9). In six of eight patients whose cancer lesions could be assessed before corticosteroid therapy for AIP, abundant IgG4-positive plasma cellular infiltration was observed in the cancer stroma. These six patients experienced no relapse of AIP after successful treatment of cancer. These data suggest that a certain portion of AIPs can be categorized as a paraneoplastic syndrome.

However, Hart et al. reported that the incidence of malignancy in 116 patients with type 1 AIP was not significantly higher than that in 344 age- and sex-matched control subjects [16]. In their study, the median follow-up was 3.6 years for patients with AIP and 3.2 years for control subjects. The proportion of patients diagnosed with cancer at any point before diagnosis of AIP (10.3%) was lower than that in the matched control subjects (17.4%). The odds of having AIP were lower in patients with cancer before the

index date compared with those without cancer (odds ratio, 0.5; 95% CI 0.23–1.08), but this was not significant ($P = 0.08$). Similarly, the risk of developing cancer after the index date was lower for patients with AIP compared with those without AIP, but this did not reach significance (hazard ratio, 0.64; 95% CI 0.272–1.51; $P = 0.31$).

An association of IgG4-SC with invasive carcinoma of the biliary tree has not been demonstrated, but some case reports have been published. Oh et al. described epithelial atypia in the common bile duct (suggestive of biliary intraepithelial neoplasia) in the presence of bile duct affection of AIP [17]. Straub et al. reported a case of intrahepatic cholangiocarcinoma arising in a patient with IgG4-SC [18].

Further observation and investigation are required to establish or rule out a possible relation between IgG4-SC and the risk of malignancy including cholangiocarcinoma.

Long-Term Outcome

With regard to long-term outcomes, whether IgG4-SC progresses to liver cirrhosis and how rapidly this could occur remain unclear. End-stage liver disease is an uncommon complication in patients with IgG4-SC [14]. A 2012 Japanese national survey of primary sclerosing cholangitis and IgG4-SC identified 43 patients with IgG4-SC who did not have pancreatic involvement (Table 19.2) [19]. The median follow-up period was 2.3 ± 1.8 years for patients with IgG4-SC. According to this survey, the 3-year survival rate was 90.0% for IgG4-SC, and liver transplantation was not performed in any of the patients with IgG4-SC (Table 19.2).

Hirano et al. reported long-term follow-up of IgG4-SC cases without steroid therapy [20]. They showed that two patients developed portal obstruction and liver atrophy, but there were no signs of liver cirrhosis or failure. Ghazale et al. reported that four of 53 patients with IgG4-SC showed portal hypertension and liver cirrhosis within 5 years of the onset of initial symptoms (Table 19.2) [8]. Three of these patients were treatment-naive at the time of diagnosis of cirrhosis and one patient was a treatment nonresponder. The time from onset of initial symptoms to the diagnosis of cirrhosis was 62, 36, and 9 months in the 3 treatment-naive patients and 26 months in the treatment nonresponder. With the exception of one patient who had a history of moderate alcohol intake, no coexisting etiologies of chronic liver disease were identified in these four patients. Death occurred in 7 of the 53 patients. The causes of death were complications of end-stage liver disease ($n = 1$), metastatic pan-

Table 19.2 Long-term outcome of patients with IgG4-SC

Reference	IgG4-SC/ IgG4-RD[a] (%)	End-stage liver disease[a] (%)	Duration from initial symptoms to cirrhosis[b] (range)	Death[a] (%)	Etiology of death[a]		Follow-up[c] (range)
Tanaka et al. [19]	43/43 (100)	0 (0)	–	3 (7)	N.A.		27.5 (6–49)
Ghazale et al. [8]	53/53 (100)	4 (7)	31 (9–62)	7 (13)	End-stage liver disease	1	N.A.
					Malignancy	1	
					Infection	1	
					Others	4	
Huggett et al. [10]	68/115 (59)	6 (5)	N.A.	11 (10)	End-stage liver disease	1	32.5 (0.8–107)
					Malignancy	4	
					Infection	1	
					Others	6	

[a]The number of patients is shown
[b]Median months of duration from initial symptoms to the diagnosis of cirrhosis are shown
[c]Median months of follow-up are shown

creatic cancer (n = 1), pneumonia and sepsis (n = 1), acute stroke (n = 1), congestive heart failure (n = 1), and unknown causes (n = 2) [8]. Huggett et al. reported 115 patients with type 1 AIP and IgG4-SC in a UK cohort and found that 68 (59%) had IgG4-SC and 6 (5%) developed liver cirrhosis during follow-up (Table 19.2) [10]. Cirrhosis was diagnosed on liver biopsy in two patients and clinically in four patients (patients with signs of synthetic dysfunction and/or hepatic decompensation with consistent radiology). One patient underwent a successful liver transplantation. Portal and/or splenic vein thrombosis developed in 9% of patients, but there was no evidence of variceal bleeding in any of the patients. Eleven (10%) patients died during follow-up. The causes of death were complications of end-stage liver disease (n = 1), cholangiocarcinoma (n = 1), transitional cell carcinoma of the bladder (n = 1), lung cancer (n = 1), cancer of an unknown primary site (n = 1), autoimmune encephalitis (n = 1), pulmonary fibrosis (n = 2), pulmonary embolism (n = 1), pneumonia (n = 1), and postoperative death (n = 1).

Collectively, IgG4-SC appears to have a favorable prognosis, probably due to the excellent response to corticosteroid therapy. However, importantly, a few cases of IgG4-SC can progress to liver cirrhosis. Further studies are required to determine the long-term outcome of IgG4-SC.

Conclusions

Recent studies have shown that patients with IgG4-SC have a favorable response to steroid treatment, but many patients experience relapse after therapy. However, because IgG4-SC is a relatively new concept, our knowledge regarding the risk of malignancy and long-term outcome is still limited. Additionally, various criteria for diagnosis, treatment response, remission, and relapse in previous studies make it difficult for comparison among studies. To resolve these problems and to obtain a better understanding about the pathophysiology IgG4-SC, further studies, including global case series and multicenter studies, are required using standardized criteria for diagnosis and treatment outcome.

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IgG4-Related Sclerosing Cholangitis in America

20

Sajan Jiv Singh Nagpal and Suresh Chari

Introduction

The first case of what has subsequently been recognized as IgG4-SC was described from the United States in 1963 in a report describing two cases of sclerosing cholangitis associated with Riedel thyroiditis and retroperitoneal fibrosis, respectively. Both patients reported in the publication underwent abdominal exploration for suspected pancreatic malignancy based on clinical and laboratory features of obstructive jaundice. However, surgery revealed a thick, firm, nodular bile duct closely resembling a thrombosed blood vessel on palpation. While one of the patients had a poor postoperative outcome, the other patient had a relapsing course requiring steroids with excellent clinical and biochemical response. The patient also had a hard mass-like lesion surrounding and occluding the bile duct, but biopsies did not show malignancy. Instead, histopathology of the bile duct explant and surrounding lymph nodes revealed inflammatory fibrosis and eosinophilia. Interestingly, these features were also seen in extra-biliary sites, i.e., thyroid and retroperitoneum in the two cases, respectively [1].

Comings et al., in 1967, reported similar findings in their patient and suggested that retroperitoneal fibrosis, mediastinal fibrosis, sclerosing cholangitis, Riedel's thyroiditis, and pseudotumor of the orbit may be the manifestations of a single underlying disease process [2]. Others also reported what was thought to be PSC with excellent response to steroids that had multiple recurrences. In this case, biopsies from the liver and intrahepatic ducts were reported as "severe sclerosing cholangitis" [3]. Over the next three decades, autoimmune pancreatitis (AIP) became much better defined as a clinical entity, and elevated serum IgG4 levels were reported to be highly sensitive and specific for its diagnosis [4]. As the concept of an IgG4-related systemic autoimmune disease (IgG4-RD) became established [5], it was also recognized that about 70% of patients with AIP have concurrent biliary involvement [6] making IgG4-SC the most common extrapancreatic manifestation of IgG4-RD.

Over the last decade, IgG4-SC has also become well established as a diagnosis distinct from PSC, and current guidelines for the diagnosis and management of PSC suggest routinely checking IgG4 levels when evaluating patients for suspected PSC [7]. However, even in patients with PSC, elevated IgG4 levels portend a worse prognosis in terms of a more severe disease course requiring liver transplantation earlier [8]. In this chapter we will focus on IgG4-SC and describe its epidemiology, diagnosis, clinical presentation, and management based on studies primarily from the United States.

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Epidemiology

IgG4-SC is the most common extrapancreatic manifestation of patients with AIP and has been described in up to 70% of these patients [6, 9]. In the absence of concurrent AIP, IgG4-SC is not only rare but can also be very difficult to diagnose. The largest and most comprehensive series of patients with IgG4-SC in the United States was published by Ghazale et al. in 2008 who described the clinical, serologic, imaging and treatment response in 53 patients with histologically confirmed IgG4-SC [10]. The mean age of the patients included was 62 ± 2 years, and the age ranged between 14 and 85 years. Most (83%) of the patients in the study were male, suggesting a significant male predominance. Forty-nine out of the 53 patients, i.e., 92% with IgG4-SC, had concurrent pancreatic involvement, and only 4 patients did not have any clinical or radiologic evidence of concurrent pancreatic disease. The presence of intrahepatic biliary strictures was the only manifestation of IgG4-SC in these four patients. In another study on patients with isolated IgG4-SC without concurrent pancreatic involvement, who were originally suspected to have cholangiocarcinoma (and underwent resection), IgG4-SC was found to affect all parts of the extrahepatic biliary tree. Diagnosis was based on operative specimens in eight out of nine patients, and only one was diagnosed preoperatively on biopsy [11]. Serum IgG4 levels were slightly elevated in three out of eight patients in the study. Studies on IgG4-SC from the United States report a slightly higher prevalence of inflammatory bowel disease (6%) in patients with IgG4-SC as compared to Japanese studies (around 4%) among patients with extrapancreatic lesions in AIP in Japan [12]. It is likely that this is due to the overall higher prevalence of IBD in the West. Interestingly, IgG4-SC is also not commonly observed in patients with IgG4-RD manifesting above the diaphragm. In a previous series of 11 patients with IgG4-positive orbital pseudotumor, only 4 had concurrent intra-abdominal manifestations of IgG4-RD (i.e., pancreas, biliary, or liver), including 1 patient with biliary cirrhosis, presumably secondary to progression of IgG4-SC [13]. Interestingly, occupational exposures (such as exposures in building contractors and plumbers) have been discovered to be risk factors for the development of IgG4-SC in adults from European studies, but there are no similar US studies describing the association [14].

Diagnosis

Patients with IgG4-SC most commonly present with features suggestive of underlying malignancy, most commonly cholangiocarcinoma [11] (especially when presenting with a focal proximal stricture) or pancreatic cancer (when associated with a distal stricture). Diffuse biliary involvement can give the appearance of PSC. While it is of paramount importance to rule out malignancy in these cases, it is also vital to distinguish it from PSC as delayed diagnosis and treatment lead to rapid progression to advanced liver disease as detailed below [8, 10]. Also, an early and reliable diagnosis can prevent major surgery in these patients, most of whom still undergo major surgery for suspected malignancy but are later found to have IgG4-RD on biopsies from the explant.

We use the HISORt (histology, imaging, serology, other organ involvement, and response to therapy) criteria for diagnosis of IgG4-RD [15]. The HISORt criteria are listed in Table 20.1. While details of the clinical presentation, laboratory, imaging, and endoscopy findings are discussed extensively in previous chapters of the book, we

Table 20.1 HISORt criteria for the diagnosis of autoimmune pancreatitis

(H) Histology suggestive of autoimmune pancreatitis
(I) Pancreatic *imaging* suggestive of autoimmune pancreatitis
(S) Serology (IgG4 ≥ 2 times the upper limit of normal)
(O) Other organ involvement
Biliary strictures, parotid/lacrimal gland involvement, mediastinal lymphadenopathy, retroperitoneal fibrosis
(Rt) Response to steroid treatment—resolution/marked improvement of pancreatic and extrapancreatic manifestations

have attempted to summarize some data from US-based studies in the relevant sections below.

Clinical Presentation

Most (70–80%) patients with IgG4-SC are known to present with obstructive jaundice, abdominal pain, and weight loss [16]. The presenting features previously reported include obstructive jaundice in 41 (77%), weight loss in 27 (51%), steatorrhea in 8 (15%), new-onset diabetes mellitus in 4 (8%), and abdominal pain in 14 of the 53 patients in the largest epidemiological study on IgG4-SC from the United States include (26%) [10]. These features are most commonly suspected to be secondary to underlying bile duct or pancreatic malignancy (especially with concurrent pancreatic involvement), and considering the rarity of IgG4-SC, malignancy should definitely be the first differential diagnosis. Patients may also have accompanying abdominal pain, but this is usually mild and does not require narcotics [10]. Patients with IgG4-SC who remain undiagnosed have a high likelihood of developing portal hypertension secondary to advanced liver disease. Out of 53 patients in the study by Ghazale et al., 4 progressed to develop portal hypertension and cirrhosis, 1 of which died from complications of portal hypertension. Three patients were treatment naive at the time of diagnosis of cirrhosis, and the fourth was a non-responder. The time from initial onset to development of cirrhosis ranged between 9 and 62 months, respectively. Two of the patients with rapid progression had previously had segmental hepatectomies. Therefore, patients with a history of prior liver surgery may be especially at risk. There are conflicting data on whether IgG4-RD increases the risk of malignancy [17, 18]. It is also not known if isolated IgG4-SC increases the risk of malignancy in the biliary tract. In our previous study, one patient died from pancreatic cancer, 5 years after the initial operation that diagnosed IgG4-SC. However, the malignancy was not found to be present on the original resection specimens upon a repeat review of the same [10].

Laboratory Findings

Liver function test abnormalities are often the first laboratory anomaly seen in patients with IgG4-SC. A cholestatic pattern of elevation is most commonly observed (i.e., raised bilirubin, alkaline phosphatase, and gamma-glutamyltransferase). In our previous study, the mean alkaline phosphatase level was 512 ± 64 U/L, and the mean bilirubin was 7.5 ± 1 mg/dL. Thirty-four percent of patients had an alkaline phosphatase level >500 U/L, and 65% of patients had bilirubin >5 mg/dL. Elevated IgG4 levels (i.e., >140 mg/dL) were seen in about 74% of patients with IgG4-SC, and 50% had values >280 mg/dL (i.e., 2× the upper limit of normal which is one of the components of the HISORt criteria). The mean IgG4 levels in the entire cohort were 516 ± 98 mg/dL (range 6–2490 mg/dL). In European cohorts, levels greater than 250 mg/dL had a sensitivity of 67–89% and a specificity of 95% to distinguish IgG4-SC from PSC. It should be noted that elevated IgG4 levels are not diagnostic, as these can be seen in patients with other inflammatory, autoimmune conditions, as well as malignancy, including cholangiocarcinoma, with or without PSC [19]. In fact, patients with PSC with elevated IgG4 levels have been reported to have a good biochemical response to steroids [20]. Unfortunately, these patients also tend to have a more aggressive disease course and a shorter time to liver transplant if treatment is delayed [8].

Other lab abnormalities that can be seen in these patients include elevated antinuclear antibodies (ANA), which are elevated in almost 50% of patients and elevated rheumatoid factor level in about 20% of patients [21] . Other inflammatory markers may also be elevated, but are not specific for disease subtype, and serum protein electrophoresis may reveal polyclonal hypergammaglobulinemia [22]. Despite advances in the diagnosis of IgG4-RD, the specific autoantibody responsible for its development remains unidentified.

Radiology

While histopathology remains the mainstay of diagnosis, characteristic radiologic clues can

point toward IgG4-SC as opposed to other causes of biliary strictures such as primary sclerosing cholangitis (PSC). In a large study from Canada, Tokala et al. described morphologic patterns of bile duct disease seen on MRI in 162 patients (47 with IgG4-RD, 73 with PSC, and 42 with autoimmune liver diseases) [23]. They concluded that the presence of continuous versus skip disease in the bile ducts, gallbladder involvement, and single-wall common bile duct thickness greater than 2.5 mm supports a diagnosis of IgG4-RD over PSC. However, IgG4-RD and PSC were unable to be distinguished based on length and location of the stricture. Despite the reported differences in radiologic appearance, it is vital to rule out malignancy by endoscopic brushings/biopsies [23].

Endoscopy

Endoscopy has a critical role in the diagnosis of IgG4-SC, predominantly because it can also help in obtaining tissue. The presence of a cholestatic pattern of liver enzyme elevation along with biliary strictures on imaging (such as MRCP) usually prompts endoscopic retrograde cholangiopancreatography (ERCP) with the intent of obtaining brushings and/or tissue to rule out malignancy. In our previous study, intrapancreatic biliary strictures, such as those seen in patients with pancreatic cancer, were present in 37 (70%) of 53 patients and were present as the only finding in 27 (51%) patients. Proximal extrahepatic biliary strictures, mimicking cholangiocarcinoma, were present in 18 of 53 patients (34%) and were an isolated finding in only 5 of 53 patients (9%). Intrahepatic strictures, similar to PSC, were found in 19 of 53 patients (36%) and were found alone in 4 of 53 patients (8%). Seventeen patients (32%) had multifocal strictures [10].

Unfortunately, the sensitivity of bile duct brushings and EUS-guided fine-needle aspiration to detect malignancy is also low. The presence of an IgG4-positive infiltrate in biopsies concurrently taken from the ampulla and pancreas might support the diagnosis of IgG4-SC, but the presence of IgG4-positive cells alone is nonspecific. Studies of biliary fluid IgG4 levels is also nonspecific as IgG4 levels may be elevated in IgG4-SC, PSC, as well as cholangiocarcinoma [24]. On cholangiography, long and multifocal strictures with mild upstream dilatation and proximal biliary involvement, with or without concurrent pancreatic involvement (i.e., diffuse pancreatic swelling and pancreatic duct narrowing), might suggest IgG4-SC. However, studies requiring experts to differentiate between IgG4-SC, PSC, and cholangiocarcinoma only reveal a 45% sensitivity of ERCP [25].

Histopathology

In our study, IgG4-SC was diagnosed histologically from a resection specimen or core biopsy based on the presence of a lymphoplasmacytic infiltrate within and around bile ducts with associated obliterative phlebitis and storiform fibrosis leading to sclerosis of the bile duct. Four patients had resection (surgical) specimens that revealed a lymphoplasmacytic infiltrate in and around the bile duct with surrounding storiform fibrosis and obliterative phlebitis, a pattern that is characteristic for IgG4-SC. IgG4 immunostaining revealed more than ten IgG4-positive cells per high-power field in all four patients. These four patients had IgG4-SC with no obvious evidence of AIP clinically or radiographically. Of the remaining 49 patients who had AIP, pancreatic resection specimens were available in 14 patients and core biopsy specimens in 15 patients. These specimens showed lymphoplasmacytic sclerosing pancreatitis (LPSP) with abundant IgG4-positive cells on immunostaining, a pattern characteristic for AIP. Endoscopic biopsy specimens of biliary epithelium were available in 16 patients. Although all specimens had adequate epithelial tissue present, a histologic diagnosis of IgG4-SC could not be made reliably based on any of these biopsy specimens. Therefore, diagnosis of IgG4-SC may remain elusive despite the availability of histopatholog-

ical specimens and bile duct brushings, especially in the absence of concurrent pancreatic involvement.

Management

As highlighted earlier, untreated IgG4-SC can progress to secondary biliary cirrhosis and portal hypertension. Therefore, early diagnosis and treatment is key. While steroids are the mainstay of treatment, there are reports of resolution of biliary strictures with the use of rituximab [26]. The emerging role of rituximab in IgG4-SC has also been discussed extensively in another chapter of the book.

Most patients with IgG4-SC have an excellent initial response to steroids. In our previous study, 29 out of 30 patients (excluding 18 that underwent surgery) demonstrated a response to steroids. Resolution of strictures and/or normalization of liver enzyme levels were seen in 18 patients (60%) and improvement in strictures and/or liver enzyme levels in another 11 patients. Unfortunately, patients with IgG4-SC have a high frequency of relapse, regardless of whether they were initially managed medically or surgically (for suspected malignancy), and patients have been reported to have relapses even during the steroid taper. Therefore, immunomodulators (azathioprine, mycophenolate mofetil, and cyclophosphamide) can be considered for the next 2 years at the end of the steroid taper, even at the initial presentation of IgG4-SC. While clinical relapses are more obvious, patients need close and continuous follow-up to assess for biochemical and radiologic relapses. A slight elevation of alkaline phosphatase may be repeated in 1–2 weeks, but if >2× elevation is seen, repeat imaging with an MRCP can be performed. If new strictures are seen, the diagnosis of a relapse is established, and the patient should be started on high-dose steroids. If no new strictures are seen, a 2-week trial of high-dose steroids can be attempted. A rapid improvement in alkaline phosphatase levels signifies a biochemical relapse, and steroids can be continued at full dose to complete for 30 days and then taper by 5 mg/week. If immunomodulators were not initiated at the initial presentation, these can be considered at this time for a period of 2 years. Some patients may have follow-up imaging that reveals new strictures. These should be considered radiologic evidence of relapse and should be managed similarly. As this condition is highly steroid responsive, the risks of continuing immunomodulator therapy beyond 2 years may outweigh the benefits, as any subsequent relapses can be easily detected and managed. However, patients need regular follow-up to ensure early detection of relapses. Factors that predict relapse are increased IgG4 levels and the presence of proximal (versus distal) strictures and might suggest the need for maintenance therapy. Also, it may be easier to maintain remission in patients with distal strictures. It should also be noted that patients on lower doses of these (i.e., azathioprine 50 mg/day and mycophenolate 500 mg twice daily) tended to experience further relapses. However, after increasing the dose to azathioprine 2–2.5 mg/Kg and mycophenolate mofetil to 750 mg twice daily, no further relapses were seen. All seven patients who had relapses managed with immunomodulators were maintained in remission during a median follow-up of 6 months (range 2–19 months) [10]. Therefore, we recommend azathioprine at a dose of 2–2.5 mg/kg to effectively maintain remission in all patients.

As stated earlier, the high frequency of relapses also suggests the need for close follow-up in these patients. Therefore, patients should have repeat liver function tests every 3 months. While a normal alkaline phosphatase level suggests remission, a significant rise (>2× upper limit of normal) should prompt reimaging to look for recurrent disease. Recurrent strictures signify a relapse and should be treated with steroids. In patients with elevated alkaline phosphatase, even if there is no radiologic evidence of recurrent disease, a 2-week trial of steroids can be useful in identifying a relapse. If there is a rapid improvement in the alkaline phosphatase, a diagnosis of a relapse can be established, and the

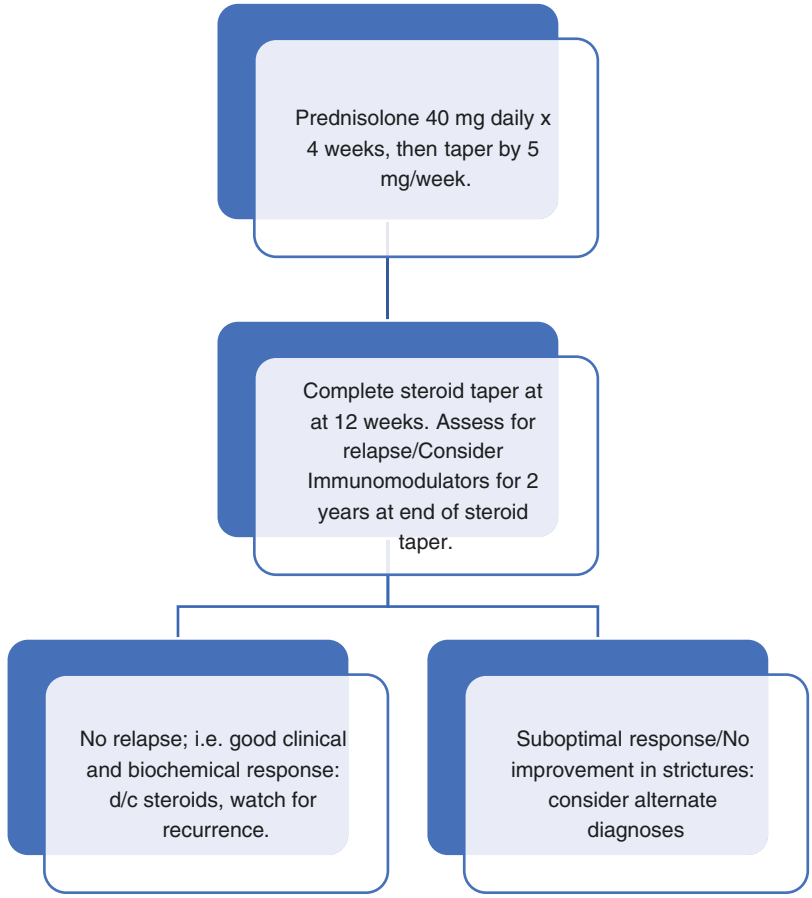

Fig. 20.1 Management of initial episode of IgG4-SC

steroids can be continued and tapered per protocol. If the patient is not already on immunomodulators, these should be considered at this point. Unfortunately, the long-term outcomes of patients with IgG4-SC are still largely unknown, and it is not clear if current management strategies prevent the development of secondary biliary cirrhosis in these patients.

A simple approach to the management of initial presentations (Fig. 20.1) and relapses (Fig. 20.2) is provided below.

Conclusions

IgG4-SC is a rare, but important mimic of other commoner hepatobiliary diseases such as PSC and more importantly, cholangiocarcinoma. While obtaining tissue for definitive diagnosis can be challenging, a definitive diagnosis can save the patient from unnecessary surgery. Initial medical management is with steroids, but there is a high likelihood of relapses, which can be managed with immunomodulators. Novel therapies include rituximab and lenalidomide, but more data is needed on the long-term use of these agents. Large, multicenter studies from the United States are needed to obtain a better understanding of this disease in the American population, especially as recognition of this disease and its treatment options progresses.

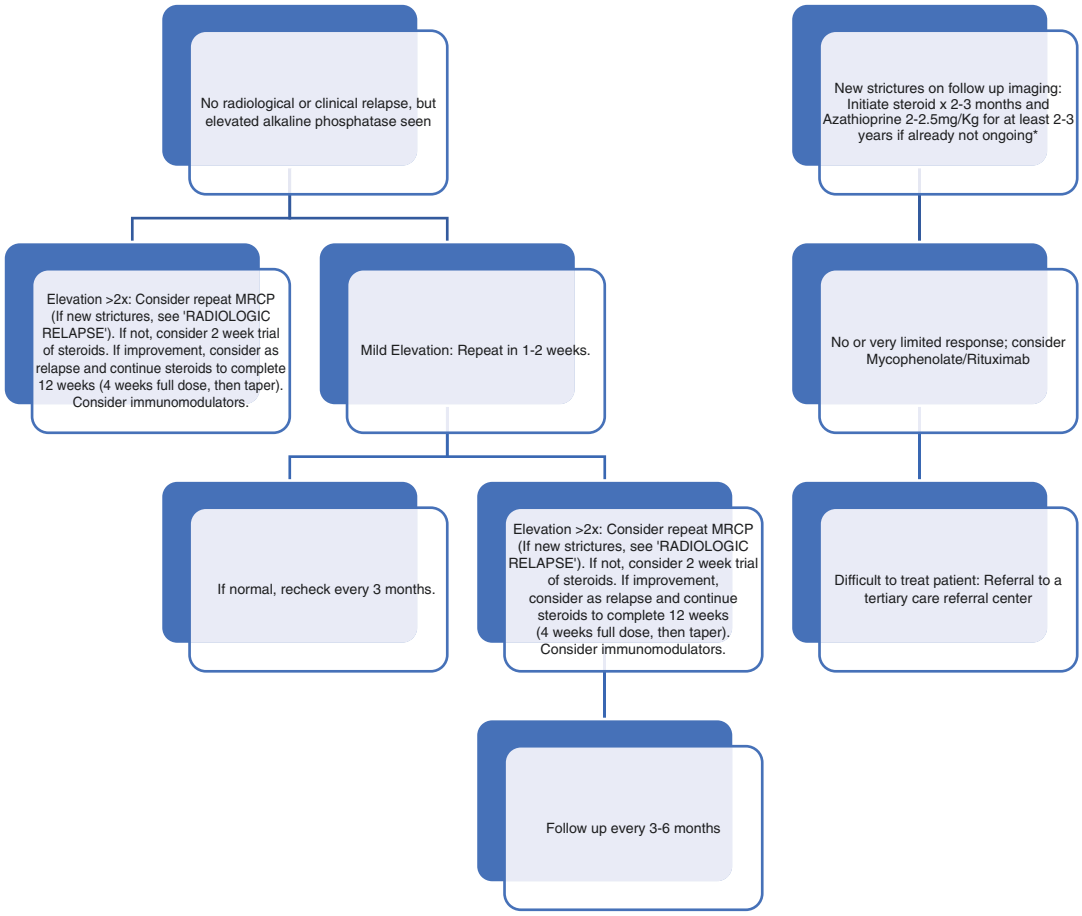

Fig. 20.2 Management of relapses of IgG4-SC. *Mycophenolate can be used for azathioprine intolerance

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IgG4-Related Sclerosing Cholangitis in Europe

21

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Introduction

Scientific interest on IgG4-related sclerosing cholangitis (IgG4-RC) is rising over the last 10 years, according to the growing knowledge on IgG4-related diseases (IgG4-RD) [1]. The term was proposed by Kamisawa et al. in 2003 [2], and autoimmune pancreatitis (AIP) is the most frequently described entity in European case series [3–6].

Only in the last few years, the approach to IgG4-RD has changed, and the concept of systemic disease has been introduced. Despite biliary involvement in IgG4-RD is more frequently reported over time, information available in Europe up to date in IgG4-RC derives from AIP series. Prospective studies focused on IgG4-RC are still lacking, probably because of its rarity. Moreover, only few hospitals in Europe are tertiary centers for IgG4-RD, and, therefore, clinical experience is limited, even in gastroenterological departments.

Very few data are available on the epidemiology of AIP type 1, IgG4-RD, and IgG4-RC in Europe. The incidence of AIP type 1 is considered rare, but no high-quality studies investigated this topic. Much more data are available in the setting of patients suffering from AIP type 1, considering that intrahepatic bile duct involvement is considered one of the most frequent extra-pancreatic manifestations in AIP patients [3–6]. However, data from different European countries appear controversial. Manfredi et al. reported biliary involvement in 37% of patients in an Italian series of AIP [7], while Maire et al. reported 10% of biliary involvement in a French study [4]. The frequency of IgG4-RC seems therefore lower in those studies than reported from Asia [8], probably because these studies have been published without differentiation between AIP type 1 and type 2. The inclusion of patients suffering from AIP type 2 (which is not considered an IgG4-RD) may explain this difference.

One of the most recent European studies on IgG4-RD, published by Hugget et al. [5], reported up to 59% of biliary involvement of AIP/IgG4-RC in UK. However, the Authors identified only 8% of patients having IgG4-RC without pancreatic involvement confirming that IgG4-RC without pancreatic involvement is quite rare in Europe. Indeed, they confirmed that the presence of IgG4-RC increases significantly the risk of relapse after steroid treatment in patients suffering from AIP.

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Clinical Presentation

Obstructive painless jaundice is the main clinical presentation of the disease [9, 10]. Other specific symptoms reported are weight loss and abdominal pain. Pancreatic symptoms are generally observed in the presence of concomitant pancreatic disease. Clinical presentation of IgG4-RC is therefore specific, and the diagnosis is challenging. Moreover, considering that IgG4-RC is generally concomitant to AIP, a primary distal biliary involvement by immune-mediated process vs. compression on the intrapancreatic common bile duct by pancreatic head inflammation is frequently difficult to differentiate. IgG4-RC has been defined for this reason as involvement only of the proximal to intrapancreatic common bile duct [5].

Diagnosis

The diagnosis is generally difficult, and the differentiation with other biliopancreatic diseases, especially pancreatic ductal carcinoma, cholangiocarcinoma, and primary sclerosing cholangitis, is crucial.

International Consensus Diagnostic Criteria are extensively accepted in Europe and are commonly used in the diagnostic work-up for AIP [11]. Because specific criteria for IgG4-RC are still lacking, ICDC are currently used even for IgG4-RC. However, considering the absence of studies focused on the applicability of ICDC in IgG4-RC patients, and the risk of misdiagnosing biliopancreatic cancers, ICDC should be used with caution in this clinical setting. Criteria for the diagnosis of IgG4-RC are generally based on morphological aspect of biliary tree, serum IgG4, and histology, when available [12, 13].

As reported above, jaundice is the main symptom in these patients, and therefore, the first diagnostic approach is generally based on abdominal US. However, a second-level imaging technique (MRI and/or CT) is needed for a complete evaluation of the biliopancreatic region. MRI with MR cholangiography is generally the most specific technique for the evaluation of the biliary system. Biliary involvement proximal to intrapancreatic common bile duct with stenosis and/or wall thickness, high serum levels of serum IgG4, or histology allows to make a definitive diagnosis of IgG4-RC, independent of the site of inflammation. In the presence of an inflammatory bowel disease and multiple biliary stenosis, a diagnosis of primary sclerosing cholangitis should be ruled out, as well as a diagnosis of cholangiocarcinoma in the presence of a single (focal) stenosis. In patients with isolated intrapancreatic bile duct involvement, the differential diagnosis of primary IgG4-RC, pancreatic cancer, distal cholangiocarcinoma, and compression on the common bile duct by autoimmune pancreatitis should be done.

Two different scenarios should be considered in the diagnostic work-up of patients with suspected IgG4-RC, based on the presence/absence of a pancreatic involvement. In patients with a diagnosis of AIP type 1 based on the ICDC, the detection of proximal biliary strictures is generally sufficient for the diagnosis of IgG4-RC.

In patients with isolated biliary abnormalities (normal pancreas), the diagnosis is much more challenging, and patient evaluation in a tertiary center is strongly suggested. Cholangiocarcinoma and primary sclerosing cholangitis are the main differential diagnosis. High serum levels of IgG4, other organs involvement by IgG4-RD, and response to steroids are useful diagnostic criteria.

EUS is used to evaluate the biliary stenosis in selected cases.

ERCP is used only for therapeutic purpose in Europe, and therefore it is not included in the diagnostic work-up.

The international consensus guidance statement on the management and treatment of IgG4-RD [14] strongly recommended a diagnostic confirmation by biopsy to exclude malignancies and other IgG4-RD mimics, with a low evidence level [5] and recommendation grade (D).

Therapy

Steroids are the main therapeutic strategy for IgG4-RC [9]. A complete and dramatic clinical and radiological response is typical, and the

response to steroids is often the cardinal criterion for a definitive diagnosis [9]. This is probably the reason why the response to steroids is observed in near 100% of cases.

Many different steroid dosages have been proposed to induce remission in IgG4-RC associated with AIP patients. Dutch authors [15] described a case series of 14 patients successfully treated with "low-dose" steroid therapy (0.2 mg/Kg). Another European study [3] reported 75 patients treated with "high-dose" steroid therapy (1 mg/Kg) with a response rate close to 99%. Similar data on steroids efficacy are reported by Huggett et al. [5] on 98 patients treated with a "medium-dose" steroids therapy (0.5 mg/Kg). Therefore, conclusive data defining the best dosage of steroids are lacking. However, the most popular approach is based on the use of "high-dose" or "medium-dose" steroids extended up to 4 weeks. After confirming the response to therapy with a new imaging procedure (MRI/CT), steroids are generally tapered by 5 mg every 1–2 weeks up to suspension. A new imaging evaluation may be considered after steroids cessation, particularly in patients with abnormal liver function tests.

The role of therapeutic ERCP in AIP and in IgG4-RC is controversial in Europe. The indication to perform ERCP with biliary stenting in IgG4-RC is the presence of jaundice with high levels of bilirubin. Some Authors treat cholestasis with biliary stenting before starting steroids [5]. However, based on the ICDC [11] and on the study of Bi et al. [16], in many European centers the strategy is to avoid biliary stenting by ERCP before starting steroid treatment, without an increased risk to develop cholangitis or other infectious complications. Rapid improvement of liver function tests is helpful for confirming the diagnosis of IgG4-RC, and normalization allows to make a definitive diagnosis.

The risk of relapse of isolated IgG4-RC is unknown, but probably it is similar to that reported in proximal biliary involvement concomitant to AIP type 1 (40%) [3, 5]. The use of an "early" maintenance therapy after the first steroid course in every patient with IgG4-RC is not recommended. The rational of this strategy is that a significant proportion of patients with IgG4-RC, with or without pancreatic involvement, will never experience a relapse.

Because of specific studies on IgG4-RC are lacking, a maintenance therapy is used is relapsing IgG4-RC, similarly to AIP type 1 patients, after a new course of steroids. Three different strategies are available in Europe as maintenance therapy in IgG4-RC: (a) low-dose long-term steroids (2.5–5 mg/day), (b) immunosuppressive drugs (e.g., azathioprine 2–2.5 mg/Kg/day), and (c) rituximab (2 doses of 1000 mg at time 0 and 15 days), which is allowed only as "off-label therapy" in selected patients and only in tertiary centers at least in Italy.

Data on long-term steroid administration have been published mainly by Japanese authors [17], and data on rituximab are reported in US studies [18, 19]. Studies from Italy and UK showed the efficacy of azathioprine to maintain remission in relapsing AIP patients with biliary involvement [5, 20]. In the absence of studies comparing long-term low-dose steroids and azathioprine, there are no clear recommendations on the type of maintenance therapy. In clinical practice the use of azathioprine is considered, particularly in patients with contraindications for steroids (intolerance, diabetes, osteoporosis). Low-dose steroids are administered if azathioprine is contraindicated or in case of azathioprine intolerance. In older patients, low-dosage steroids is preferred considering the increased risk for any cancer in this population.

The experience on rituximab is limited to few centers in Europe. Rituximab is generally administered based on the rheumatological protocol (repeated at 6 months). This therapy is applicable in Europe only after failure/intolerance of "standard maintenance therapy" with azathioprine/steroids. In our experience, rituximab is effective in maintaining remission in relapsing AIP type 1 ± IgG4-RC, but no published data are available in Europe.

Conclusion

Specific experience on IgG4-RC is limited to few tertiary centers in Europe, and high-quality studies are lacking. Therefore, ICDC are considered the best diagnostic criteria not

only for AIP but even for IgG4-RC. Steroids are considered the best therapeutic option as induction therapy, despite the absence of definitive data on the best dosage. This explains the great differences in dosage of steroids in different European centers. Standard maintenance therapy in all patients is generally not suggested but reserved to relapsing disease. Azathioprine is a therapeutic option as well as long-term low-dose steroids. Rituximab is available only as off-label second-line option in relapsing patients intolerant or not responding to azathioprine. Multicenter prospective studies are needed for establishing the best therapeutic strategies in patients with IgG4-RC.

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22 Pathophysiology-Based Approaches to Treatment

Cory A. Perugino and John H. Stone

Introduction

IgG4-related disease (IgG4-RD) is an immune-mediated, fibroinflammatory condition that can affect nearly any organ system [1]. The biliary tract is often targeted, typically in association with type 1 autoimmune pancreatitis. The first line of therapy for IgG4-RD in general and for hepato-pancreatico-biliary disease specifically has been glucocorticoids. Glucocorticoids generally induce remission in a high proportion of patients with IgG4-related hepato-pancreatico-biliary disease but have not been investigated thoroughly in randomized controlled trials. The application of systemic glucocorticoids to patients fitting the typical demographic profile of IgG4-RD—namely, middle-aged to elderly individuals, often prone to other comorbidities—is often problematic. Moreover, given the predilection of patients with IgG4-related sclerosing cholangitis to have simultaneous pancreatic dysfunction, treatment with glucocorticoids poses other challenges in the context of glucocorticoid-induced diabetes.

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To date, although disease-modifying antirheumatic drugs (DMARDs) are often used in the hope of reducing glucocorticoid dependency, there is a paucity of data to suggest that these medications actually provide any benefit beyond that which is observed with glucocorticoids alone. All of the above considerations underscore the importance of exploring new approaches to the treatment of IgG4-related sclerosing cholangitis. Particularly desirable would be the development of medical therapies rooted in a firm understanding of disease pathophysiology. In this regard, the potential for devising new treatment approaches is bright, for even over the short period of time in which IgG4-RD and its associated hepato-pancreatico-biliary disease have been known to exist, much has been learned about the pathophysiology of this condition.

In this chapter, we consider possibilities for new medical treatment approaches to IgG4-related sclerosing cholangitis, based on the current understanding of its pathophysiologic features. We begin with an overview of the current state of IgG4-RD treatment as it relates to glucocorticoids and non-biologic DMARDs.

Glucocorticoids in IgG4-RD

Glucocorticoids are typically employed in both remission induction and remission maintenance modes in IgG4-RD.

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Glucocorticoids for the Induction of Remission

Glucocorticoids are highly effective agents for establishing prompt disease control in IgG4-RD. Patients' response to glucocorticoids—generally on the order of 40 mg/day of prednisone—is swift and leads to disease remission in the majority of cases, particularly if the drugs are employed in moderately high doses for a period of 4–8 weeks. A retrospective, multicenter study in 25 IgG4-RD patients in France demonstrated that a starting daily dose of prednisone of approximately 47 mg, equating to 0.67 mg/kg for a 70 kg patient, was effective in controlling the disease in 90% of patients [2]. The investigators in that study defined treatment response as the presence of at least two of the following features: improved clinical status, reduction in serum IgG4 concentration, and improved radiologic findings. Even higher response rates have been reported in autoimmune pancreatitis [3–5]. Another retrospective study examined the effect of prednisone in 30 patients with IgG4-related sclerosing cholangitis and found that 97% of patients experienced either improvement or resolution of strictures and liver function tests on treatment [6]. Such studies support the use of glucocorticoids as a cornerstone of remission induction efforts [7]. A number of important caveats to the use of glucocorticoids exist, however. These are discussed below, under Glucocorticoid-Related Side Effects.

Glucocorticoids for Remission Maintenance

A widely used regimen for the initiation of glucocorticoids is a 2–4-week course followed by a gradual taper [7]. Some studies have employed a taper of 5 mg per week discontinuation [2, 3, 6]. Another regimen includes tapering by 10 mg every 2 weeks until the achievement of a daily dose of 20 mg, continuing 20 mg/day for 2 weeks, and then continuing to taper by 5 mg every 2 weeks discontinuation [7]. Whereas Japanese clinicians often continue prednisone at a low to moderate dose (2.5–10.0 mg daily) for up to several years, the practice in North America is to taper the glucocorticoid completely off within 2–3 months [8].

Glucocorticoid-Related Side Effects

Two major issues with regard to glucocorticoid therapy are pertinent. First, baseline comorbidities and frailties often make IgG4-RD patients poor candidates for long-term glucocorticoid therapy. A substantial proportion of patients with IgG4-RD, usually a disease of middle-aged to elderly individuals, suffer at baseline from obesity, glucose intolerance, hypertension, osteoporosis, and other relative contraindications to prolonged glucocorticoid courses. Moreover, autoimmune pancreatitis often leads to endocrine as well as to exocrine insufficiency, further complicating glucocorticoid treatment.

A single-arm prospective trial of glucocorticoid treatment alone from Japan maintained patients on doses of prednisone between 5 mg/day to somewhat higher than 10 mg/day. The duration of follow-up in that trial was 1 year. That trial reported disease control in 67% of patients, but 28% developed either new diabetes or exacerbations of previously known diabetes, and there were a variety of other serious complications of long-term glucocorticoid treatment, including infections [9]. In the cohort of patients from France described above, 67% of patients experienced side effects from glucocorticoid therapy [2]. Thus, the comorbid conditions of each patient and the potential for glucocorticoid intolerance must be considered on an individual basis when deciding on the suitability of treatment, as well as the initial dose and duration of glucocorticoid therapy. To date, no study has a starting dose of prednisone calculated to control the disease and then followed prospectively through a prescribed prednisone taper to discontinuation of the medicine.

The second major point of relevance with regard to glucocorticoids is that although only a minority of patients fail to respond to glucocorticoid treatment, a large percentage relapse during

or after the glucocorticoid taper. Between 30% and 60% of patients relapse within 3 months of discontinuing glucocorticoid monotherapy in the absence of remission maintenance therapy [3, 5]. Even with low-dose maintenance glucocorticoids studied retrospectively in patients with autoimmune pancreatitis, 23% relapsed while on treatment [5]. Thus, the substantial risk of adverse effects from glucocorticoids and their failure to provide sustained disease control at doses that are tolerable from the perspective of safety are major inducements to the search for new therapies.

Conventional DMARDs in IgG4-RD

A group of international IgG4-RD experts collaborating on a 2015 Consensus Guidance Statement on the Management and Treatment of this condition concluded that few data support the use of conventional steroid-sparing agents in IgG4-RD [7]. In the largest study of therapy published to date, in fact, no benefit of adding a DMARD to glucocorticoids was observed in terms of relapse-free survival [10]. The enthusiasm of these authors for DMARD therapy as potential steroid-sparing agents is low.

A Consideration of IgG4-RD Pathophysiology

Overview

The pathophysiology of IgG4-RD involves a series of interactions between various cells of the B and T cell lineages, including B cells, plasmablasts, plasma cells, $CD4^+$ CTLs, and follicular helper T (Tfh) cells—in addition to communications among myofibroblasts, macrophages, and eosinophils. The sum of these pathways leads to the histopathological findings characteristic of IgG4-RD in essentially every organ system: a lymphoplasmacytic infiltrate, frequent mild to moderate tissue (as well as peripheral) eosinophilia, obliterative phlebitis (and occasionally arteritis), and storiform fibrosis.

Concept of a Th2-Mediated Pathophysiology is Out of Favor

The original notion that IgG4-RD is a Th2-mediated disease has now been largely debunked. Circulating $CD4^+$ $GATA3^+$ T lymphocytes produce stereotypic Th2 cytokines (IL-4, IL-5, IL-13) only in patients who have longstanding atopic histories antecedent to their clinically evident IgG4-RD [11]. Moreover, the expansions of Th2 cells taken from the blood of patients with IgG4-RD are polyclonal, a reflection of their lifetime exposure to environmental allergens rather implicating a response to a specific triggering antigen [11].

Plasmablasts and the Cells Driving the Class Switch: T Follicular Helper Cells

Plasmablasts, defined by cell surface expression of CD19, CD27, and CD38 but negative for CD20, are dramatically elevated in the peripheral blood of patients with IgG4-RD who have not received treatment [12, 13]. These plasmablasts are oligoclonally expanded, express IgG4, and show intense somatic hypermutation [12]. They also respond swiftly to B cell depletion and demonstrate clonal divergence upon reconstitution. A subset of Tfh cells appears to drive the class switch within germinal centers through the elaboration of IL-4.

The Linchpin: A $CD4^+$ Cytotoxic T Lymphocyte?

Both the peripheral blood and affected tissues of patients with IgG4-RD demonstrate oligoclonal proliferations of a novel $CD4^+$ effector-memory T cell [14]. These effector-memory T cells demonstrate both modified Th1 cytotoxic lymphocyte signatures and myeloid cells signatures [14]. These cytotoxic T lymphocyte (CD4 CTL) cells demonstrate striking oligoclonal expansion by next-generation sequencing [14]. The implication is that in any given patient, IgG4-RD is likely

to be triggered by an antigen—or perhaps a collection of antigens, different from patient to patient—that stimulates the CD4 CTL expansion observed. These $CD4^+$ CTLs have been shown to elaborate a number of powerful cytokines known to mediate fibrosis, namely, transforming growth factor beta, interferon gamma, and interleukin-1 beta. These cells could therefore serve as the primary driver of the storiform fibrosis that is such an important part of the pathology of IgG4-RD.

What of the IgG4 Molecule Itself?

Orthodox thinking about IgG4-RD has always held that IgG4 differs from other IgG subclasses by its relative inability to fix complement (at least via the classical pathway of complement activation) or bind Fc receptors and that it is therefore better suited to a counterregulatory immune response. Concordant with this traditional thinking about IgG4, once postulated to be at the center of the disease with regard to pathophysiology, this molecule is now believed (somewhat ironically) to subserve a far less important role than the one originally conceived for it in IgG4-RD. The principal role of IgG4 in IgG4-RD appears to lie not in an association with the primary immune response but rather in an ineffectual effort to suppress the primary response.

In summary, the current model of pathophysiology not only explains in large measure the known efficacy of certain medications (e.g., glucocorticoids and rituximab), it also provides the rationale for other potential treatments. In this context, we discuss current and future treatment options for patients with IgG4-RD.

B Cell-Targeted Therapy in IgG4-RD

The discovery of oligoclonally expanded plasmablasts in patients with IgG4-RD [12] and their correlation with disease activity [13] elucidate further how targeting cells of the B cell lineage might work in IgG4-RD (and other diseases). Plasmablasts, circulating plasma cells that arise from activated $CD20^+$ B cells, are antibody-secreting cells and typically develop into tissue-based plasma cells. Rituximab functions via antibody-dependent cell-mediated cytotoxicity, leading directly to B cell depletion, thereby eliminating plasmablasts' progenitors. Despite lacking CD20, plasmablasts decline quickly following rituximab administration. The decline of these cells—and perhaps more importantly their recurrent rise over time in some patients—correlates better with disease activity than does the serum IgG4 concentration [12].

The potential utility of rituximab in IgG4-RD was demonstrated initially in case series [15, 16] and then in a prospective, open-label trial involving 30 patients [17]. Seventy-seven percent of the patients enrolled achieved the primary outcome in the trial, defined as a decline in the IgG4-RD responder index (IgG4-RD RI) of ≥ 2 points, no disease flares before 6 months, and no glucocorticoid use between months 2 and 6. Twenty-six of the 30 patients enrolled were treated without glucocorticoids, yet 29 of 30 a therapeutic response. Moreover, 47% achieved a complete remission at 6 months, defined by an IgG4-RD RI of 0 and no additional glucocorticoid treatment [17].

In addition to interfering with antigen presentation by plasmablasts, B cell depletion may also achieve its effect through the reduction of immune complex formation. The potential importance of immune complex formation as a possible disease mechanism has yet to be studied thoroughly in IgG4-RD. This may be particularly relevant for those patients with hypocomplementemia and the associated manifestation of tubulointerstitial nephritis (TIN) [10]. The phenomenon of immune complex formation in IgG4-related disease remains incompletely understood, yet seems to be operative in some organ manifestations—particularly IgG4-related TIN. IgG4 does not bind complement well under most circumstances but other IgG subclasses that are often elevated to a lesser but still substantial extent in IgG4-RD. As examples, elevations in IgG1 and IgG3 might easily account for this observation. Moreover, the mannose-binding lectin pathway of complement activation is a

possible mechanism whereby IgG4 could also trigger this phenomenon itself.

Treatment with rituximab usually leads to symptomatic improvement within 1 month, a swift decline in serum IgG4 concentrations, and the ability to discontinue glucocorticoids entirely within a few weeks in most patients [15–17]. Blood plasmablasts have some utility for monitoring disease activity and gauging the need for potential retreatment [13] but are more likely to be elevated to a striking degree in patients who have never been treated before.

Plasmablasts as a Target of Treatment

Therapies targeting plasmablasts may offer a more specific approach to treating IgG4-RD. XmAb5871, a monoclonal antibody (homodimer) with a high-affinity variable region binding to CD19 and an enhanced Fc domain that binds to the FcγRIIb inhibitory receptor of B cells, is currently in phase II development for IgG4-RD treatment. This nondepleting anti-CD19 therapy has been studied in phase 1 trials and mechanistic studies in both rheumatoid arthritis [18] and systemic lupus erythematosus [19]. The rapid on/off effect of Xmab5871, its fully humanized structure, and its status as a nondepleting antibody may pose potential advantages over rituximab.

Future Therapeutic Directions

$CD4^+$ CTL-Directed Treatments

Oligoclonally expanded $CD4^+$ effector-memory T cells with a cytotoxic phenotype ($CD4^+$ CTLs) have been identified and characterized recently in IgG4-RD [14]. The clonal expansion, pro-fibrotic phenotype, and correlation to disease activity of these cells are consistent with a central role in the pathophysiology of IgG4-RD. These cells express SLAMF7, IL-1β, TGF-β1, granzyme B, and perforin. Despite their lack of CD20 expression, the concentrations and percentages of the overall T cell pool of these novel $CD4^+$ CTLs decreased substantially following rituximab administration. The responsiveness to CD20-targeted B cell depletion is theoretically related to the interference of T and B cell collaboration as plasmablasts present antigen and activate effector-memory CD4 CTLs at the site of inflammation.

Anti-fibrosis Therapies

Some IgG4-RD patients have a substantial burden of fibrosis even at the time of diagnosis. The fibrotic features are unlikely to respond to the currently available therapies and are therefore in great need of therapies designed specifically to address fibrosis. Some data indicate that the fibrosis of IgG4-RD may in many cases be at least partially reversible. A decrease in both circulating markers of fibrosis and myofibroblast activation in the affected tissue following rituximab therapy has been observed [20]. Evidence also comes from both studies of posttreatment tissue samples in the laboratory [20] and from serial clinical evaluations—particularly chest imaging—of patients following the institution of treatment. The impact on fibrosis of Xmab5871 and potential future therapies such as those directed against the $CD4^+$ CTL remain uncertain at the moment, but such effects will be a key aspect of the evaluation of any new treatment agent.

Conclusion

The rapid progress in understanding the pathophysiology of IgG4-RD has led to several exciting mechanism-based therapies for IgG4-related sclerosing cholangitis. These include B cell depletion, a first-in-class homodimer targeting both CD19 and FcγRIIb, and the possibility of directing therapy against a novel $CD4^+$ CTL that may be at the heart of this condition. Other potential therapeutic approaches will certainly emerge as our understanding of the pathophysiology of IgG4-RD becomes even more detailed.

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